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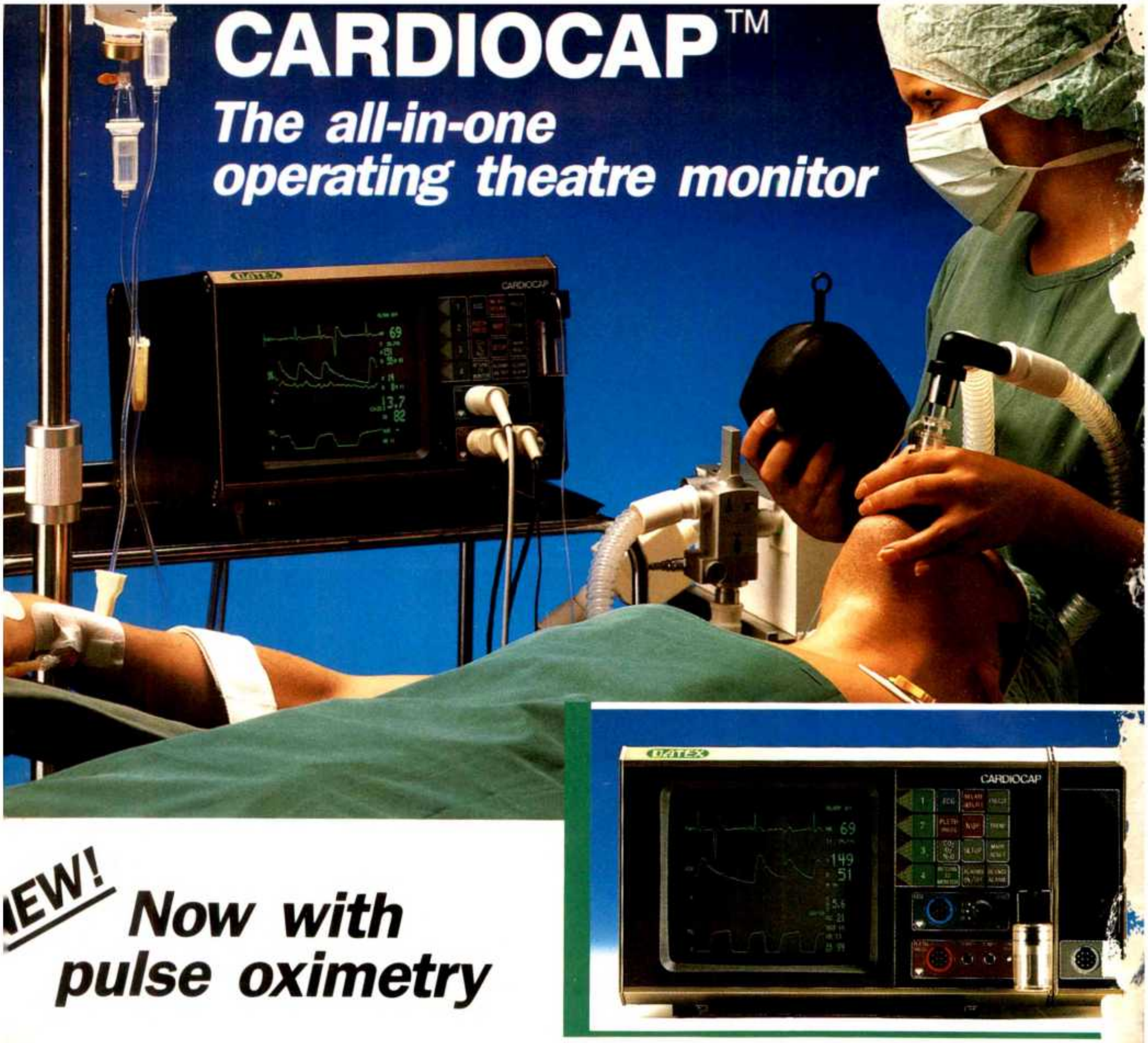

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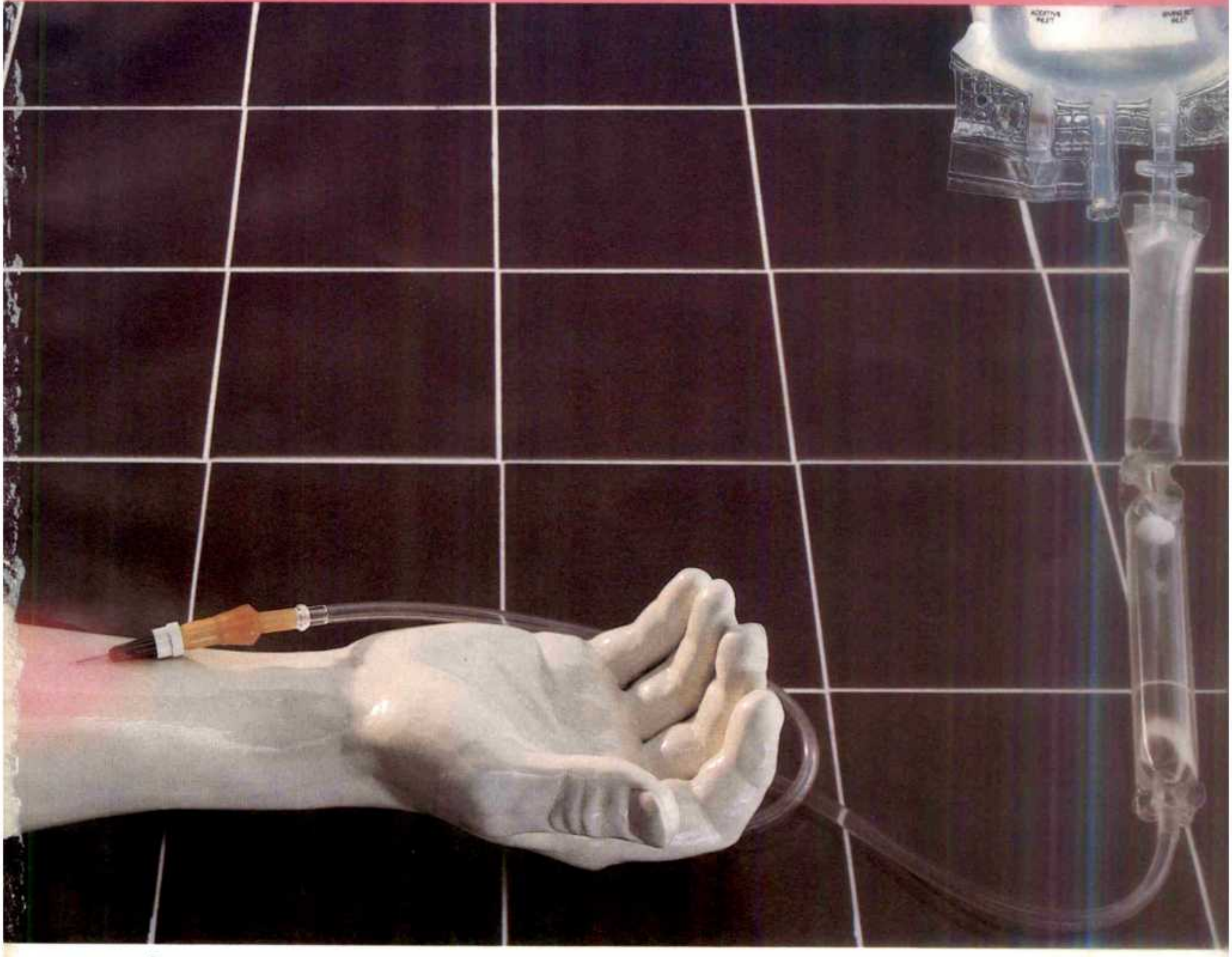

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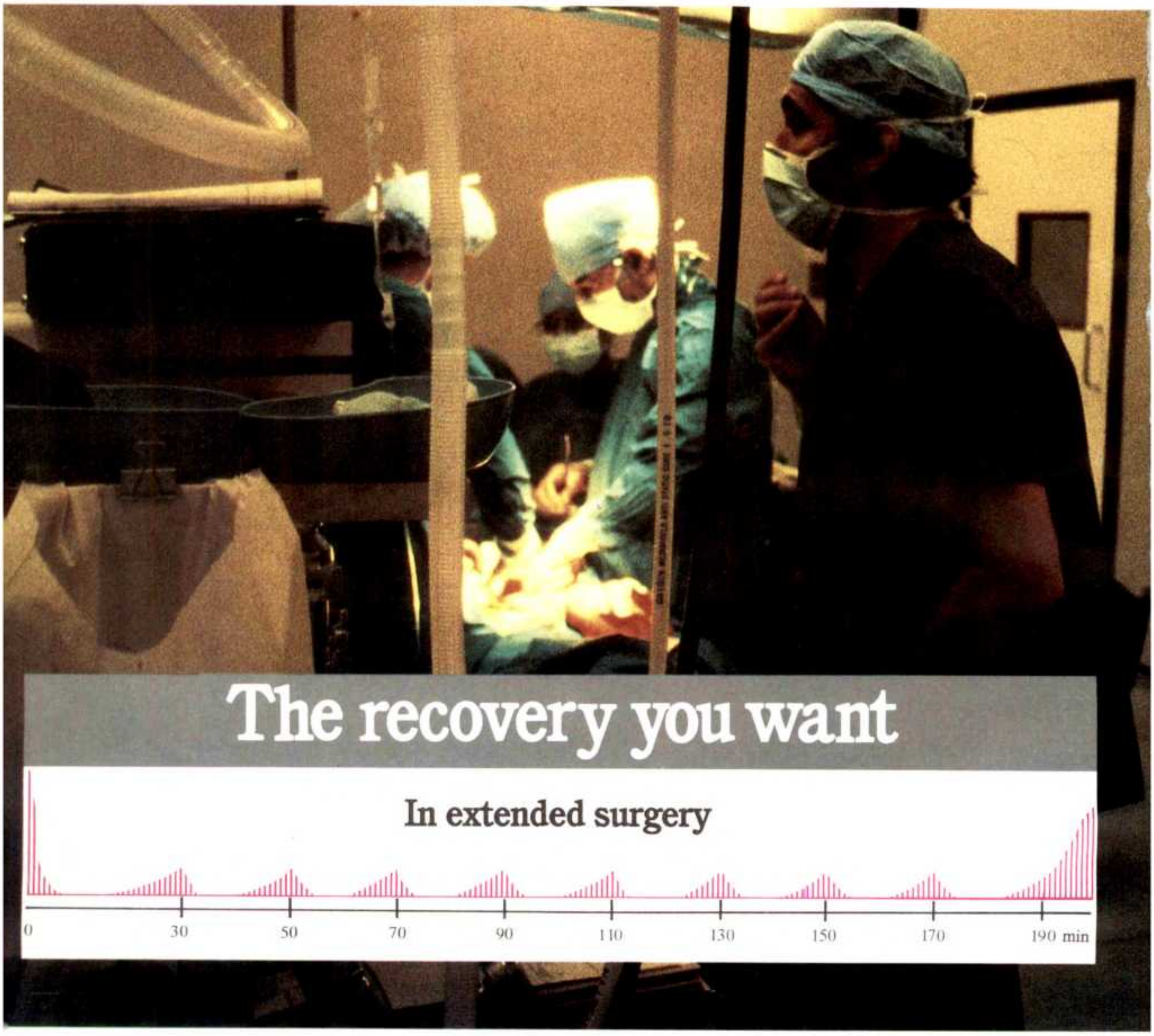

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1. Data on file, Wellcome, 1987.
2. Yate, P.M. *et al.* (1986), *Br. J. Anaesth.*, **58**, 112 S.

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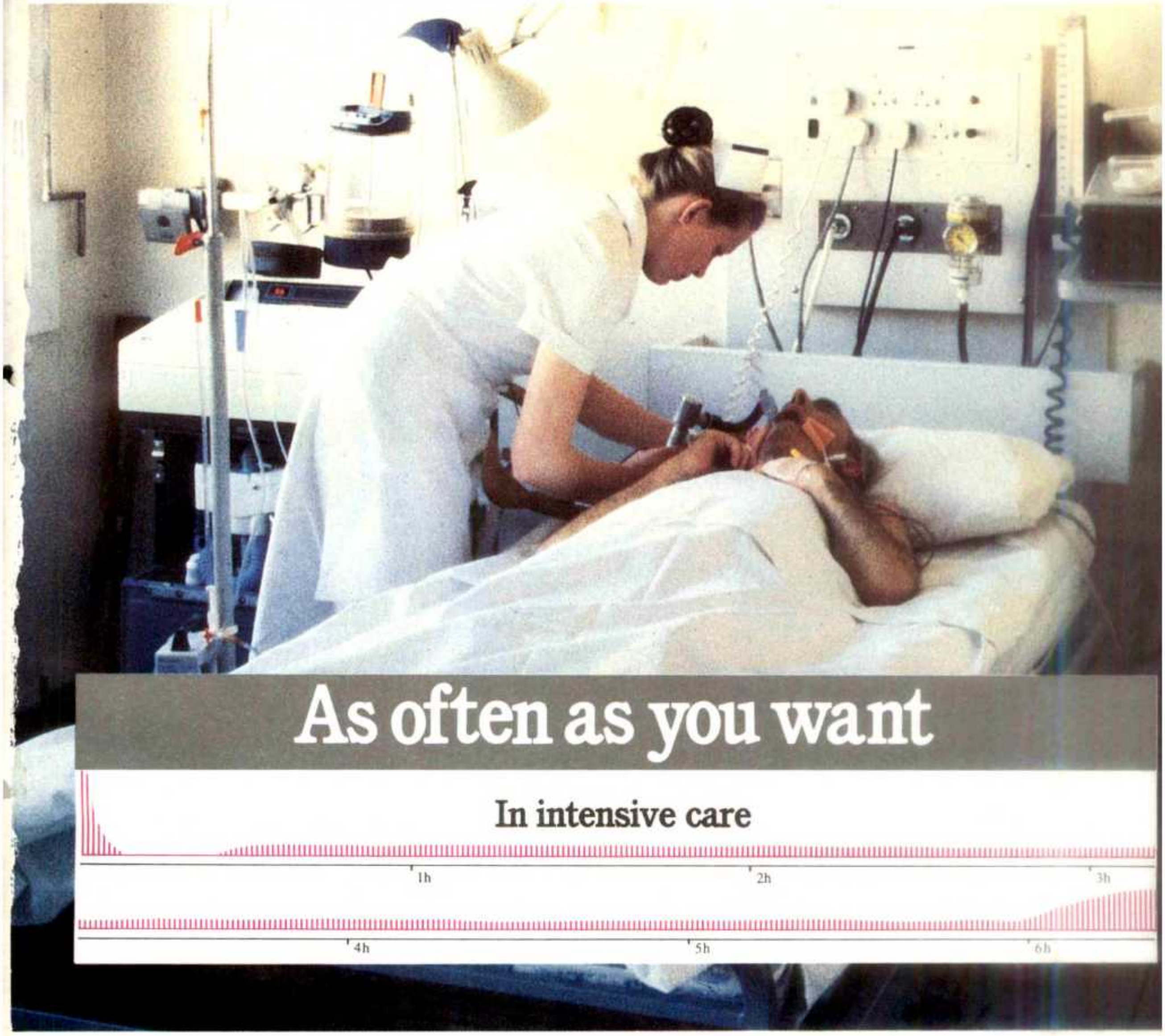

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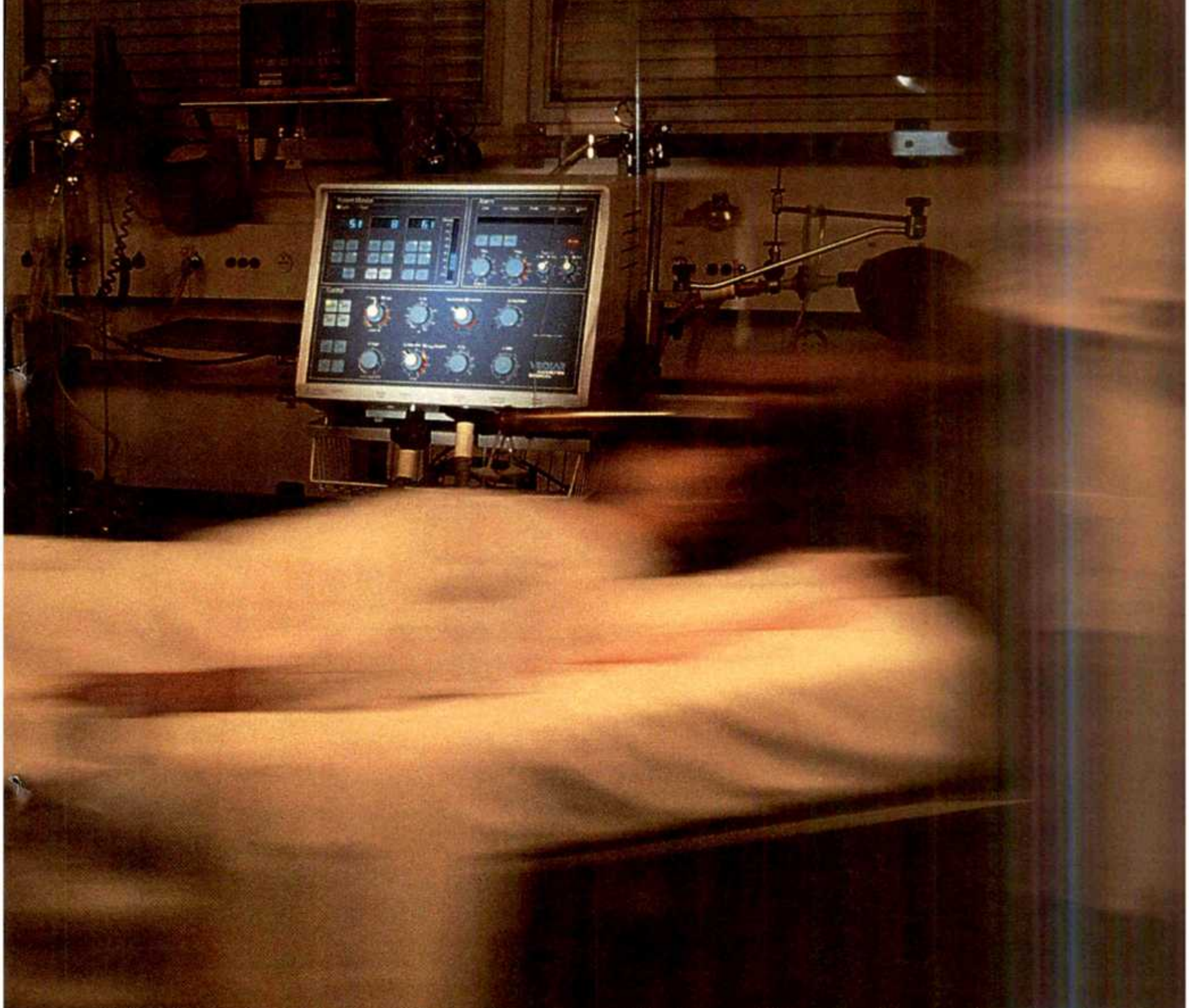

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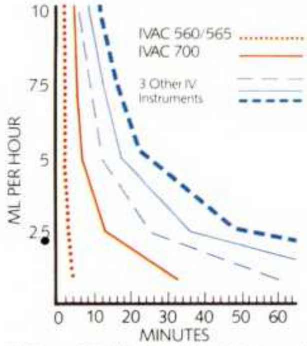

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Instructions to the printer. Words to be printed in lower-case italics should be indicated by one underline. Two underlines indicate small capitals, three indicate large capitals and four, italic capitals. A wavy underline indicates a word to be printed in bold type.

Headings in the text. Six possible grades are available, and may be indicated by the following letters of identification:

A	PART I	(capitals)
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C	Blood-Gas Analysis	(l.c. roman)
D	*The Action of Drugs*	(italics, centre)
E	*Lung function studies*	(italics, full out)
F	*Volume.* Large volumes...	(italics, indent)

Symbols and Abbreviations. In accordance with Editorial adoption of SI Units, abbreviations and symbols should follow the conventions described in the booklet *Units, Symbols and Abbreviations. A Guide for Biological and Medical Editors and Authors* (ed. G. Ellis), published by and available from The Royal Society of Medicine, 1 Wimpole Street, London, W1M 8AE. Words for which abbreviations are not included should be written in full at first mention in the summary and again in the text and followed by the abbreviation in brackets. This will usually be in the form of large capitals without separating points.

Spelling, etc. British spelling should be used with "z" rather than "s" spelling in, e.g. organize, organization.

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It is proposed that a proportion of the Journal be devoted to correspondence each month. Every effort will be made to ensure that correspondence arising from papers in a recent issue is published without delay, and for this reason, relevant correspondence will be given priority over that pertaining to original research. Authors of correspondence concerning original work will receive proofs at the Editor's discretion.

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1. Feldman SA; Clinical Experiences with Norcuron, Excerpta Medica (1983) 199-200
2. Basta SA; Clinical Experiences with Norcuron, Excerpta Medica (1983) 183-184

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The International Anesthesia Society,
3645 Warrensville Center Road,
Cleveland, Ohio 44122, U.S.A.

ERRATUM

Br. J. Anaesth. (1987), **59**, 929P

The final paragraph of the abstract by Wetherill and Spence should be replaced by:

These results suggest that continued uptake of nitrous oxide over the period of observation is involved in the stabilization of oxygen concentration within the nitrous oxide–oxygen system and provide further support for the use of 1 litre min^{-1} as a practicable means for delivering nitrous oxide in oxygen mixtures safely at low flow rates.

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Ohmeda Technical Report

Insurance against signal interference: detection and minimization in pulse oximetry.

Pulse oximeters rely on plethysmographic pulsations to determine oxygen saturation levels.[1] There is no doubt that signal interference in pulse oximetry monitoring can cause erroneous SaO_2 readings. This interference has been well documented.[2,3,4] Because of the inescapable phenomenon of signal interference, two capabilities are required in pulse oximetry technology.

The first requirement: continuously displayed plethysmographic waveform.

Pulse oximeters that display an arterial plethysmographic waveform have an advantage over those that display only the pulse amplitude of the signal. The waveform allows the operator to assess the quality of the signal from which the arterial oxygen saturation is derived, and to observe noise, which may alter its accuracy.[5]

The value of a waveform is that you can tell if you are getting a real physiological signal.[6] With a displayed arterial waveform or plethysmograph, interference is easily detected by the shape of the waveform. On a non-waveform oximeter, a bouncing pulse indicator does not give the clinician any information on the integrity of the shape of the arterial waveform. Interference from a fiberoptic light source, surgical lighting, or infrared heat lamps might go undetected, and erroneous SaO_2 readings might be accepted as valid.[7,8,9]

The second requirement: selective signal processing. Quantity, weighting, and averaging.

Pulse oximeters that make multiple readings during the cardiac cycle, rather than a single calculation at the peak and trough, have more data to compensate for artifactual changes.[10]

The Ohmeda pulse oximeter performs thirty SaO_2 calculations every second, rather than one per beat, so that enough data are provided for intelligent, selective processing. The objective is to gather enough data to permit some discrimination during selective processing, while maintaining a rapid response time. Selective processing is then done by "weighting" each SaO_2 calculation and "averaging" the weighted data.

Weighting.

With this large number of data points, it is possible to selectively "weight" each one. The Ohmeda pulse oximeter uses many criteria to qualify the validity of each data point and determine the appropriate weight. These include the magnitude of change in the amplitude of the waveform, the point in the cardiac cycle, the "newness" of the data, and the correlation to the present "average" saturation.

Example: When interference is present, the "noise" spikes typically have extreme amplitude changes. Consequently, the weighting of these unnaturally large amplitudes is lower, thereby minimizing the effect of interference.

Example: Interference can cause the instantaneous SaO_2 value to be significantly different than the current "average" saturation, so these outlying SaO_2 values are weighted lower. The greater the difference, the lower the weighting.

For instance, if the present "average" saturation is 96% and the next data point is calculated to be 72% (due to interference compromising the calculation), this data point will be given a low weight. If an instantaneous value of 50% is calculated, it will be given an even lower weight. Intuitively, we know this dramatic change in the patient's saturation could not occur in 1/30th of a second.

The weighting factor allows a discounting of physiologically implausible differences in each instantaneous SaO_2 value, thereby reducing the effect of interference on displayed SaO_2 readings—without the additional confusion of ECG leads, extra cables, and heavy interconnect boxes.

Averaging.

The individually weighted data points are then averaged over a selectable 3, 6, or 12 second interval. In a six-second period, the oximeter has 180 data points from which to calculate SaO_2. If a very fast response or optimum resolution in SaO_2 changes is necessary, the faster three-second response mode is available. During periods of prolonged interference, the capability to extend the averaging time allows for the collection and weighting of enough data to derive a valid, stable saturation reading.

In monitoring SaO_2, it is necessary to have reliable readings for patient safety. Signal interference can be detected and minimized with optimal data collection, signal processing, and continuous waveform display.

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[1] Unprecedented Rise in Use of Pulse Oximetry Reflects Important Advance in Anesthesiology. **Anesthesiology News,** July 1987, pp 1, 66, 68–69. [2] Block FE Jr. Interference in a Pulse Oximeter from a Fiberoptic Light Source. **Journal of Clinical Monitoring,** July 1987, pp 210–211. [3] Pulse Oximeter Interference from Surgical Lighting. **Health Devices,** February 1987, pp 50–51. [4] Brooks T, Paulus D, Winkle W: Infrared Heat Lamps Interfere with Pulse Oximeters. **Anesthesiology,** November 1984, p 630. [5] Taylor MB, Norley I: Correspondence "Erroneous Actuation of the Pulse Oximeter." **Anaesthesia,** 42:10:116, October 1987. [6] Gravenstein NS: Technical Note. **Oximetry Update,** Edition 3, Summer 1986. [7] Same as footnote 2. [8] Same as footnote 3. [9] Same as footnote 4. [10] Same as footnote 1.

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Abbott Laboratories Limi

"I would have everie man write what he knowes and no more."—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 60, No. 1 JANUARY 1988

EDITORIAL

EDITORIAL CHANGES IN BRITISH JOURNAL OF ANAESTHESIA

Although the new editorial team has been involved in the processing of manuscripts submitted to *British Journal of Anaesthesia* since August 1987, this issue marks the formal transfer of the editorial office of the Journal from Glasgow to Leicester. This process will be accompanied by changes in both the editorial team and, to a small degree, the format of the Journal.

First, however, the incoming Editor would wish to pay tribute to Dr W. Fitch, who will retire as Joint Editor in March 1988. Dr Fitch has presided over the Journal as Editor during a period which has seen an unprecedented increase in the number of manuscripts submitted and also a change in working practice of the Editorial office by expansion of the editorial team to include two Associate Editors. We are indebted to Dr Fitch for having instituted these changes smoothly and efficiently and for having undertaken the enormous workload involved in being Editor with his usual modesty and quiet efficiency.

Of the changes to be introduced by the new Editor, the most obvious to the reader is the use of the Vancouver style of referencing. This was publicized in the Journal in September 1987, and all new manuscripts now submitted for consideration of publication are obliged to follow this format which, for the uninitiated, is described in the Guide to Contributors contained in each issue of the Journal. Although the Vancouver style is not the personal preference of all readers, we believe that there were good indications for initiating this change; amongst the many reasons for doing so must be included standardization with the majority of other anaesthetic journals published worldwide.

The other major change which will take place concerns Postgraduate Educational Issues. Until the present time, the Journal has published two educational issues per annum, normally in January and July. In these issues, we have attempted to review a broad topic by means of 8–10 articles commissioned from national or international experts in their respective fields. However, there are many subjects, important and topical, which may form the basis of an excellent single review article but which cannot constitute a whole issue of the Journal. For this reason, whenever possible in future, we plan to incorporate such a review article in every general issue of the Journal. In order to keep the total amount of original material constant, this change will necessitate a reduction in the number of postgraduate issues from two to one per annum, the issue being published normally in July or August. For the present year, however, we shall publish two educational issues, the first appearing as an additional volume in late February, and devoted to the topic of Malignant Hyperpyrexia; the second postgraduate issue will appear in July and will cover the topic of Anaesthesia and Myocardial Ischaemia. Thus there will be 13 standard issues (general plus educational) of the Journal published in 1988, and we shall revert to 12 issues in 1989. The Journal will, of course, continue to publish supplements, usually sponsored, provided that the manuscripts proferred meet our editorial standards.

In the past, *British Journal of Anaesthesia* has possessed a reputation amongst some of our readers of being somewhat esoteric and carrying research biased towards laboratory rather than clinical investigation. This impression may have been reinforced by the categories "Clinical Investigation" and "Laboratory Investigation" which have been used in the past. This distinction will now be abandoned in favour of a single category termed "Original Articles", since analysis of recent volumes of *British Journal of Anaesthesia* suggests that the overwhelming predominance of scientific material published relates to clinical research. In addition, we aim to introduce a new category of article, the Short Communication, which will have the form of a summary, an introduction, a methods and results section, and finally a comment. The short communication should contain not more than six references, not more than one table *or* figure, and constitute not more than one and a half pages of printed page (1200 words). The use of this format should enable us to carry a larger number of original manuscripts. These manuscripts will be processed in the same manner as all articles submitted to the Journal, requiring expert opinions from at least two consultant assessors, but brevity of the script should enable the assessment to be carried out more rapidly and this might, therefore, expedite the speed of publication. We do hope that intending authors give serious consideration to this format as a mode of communication for their work.

We also continue to encourage readers to submit case reports to *British Journal of Anaesthesia*, but it is important to appreciate the reasons why such reports may be rejected as unsuitable for publication. The purpose of a case report is not to document for posterity a laudable and outstanding struggle in which the anaesthetist has managed against all odds to care for a patient safely, despite the hazards of potentially fatal medical illness or over-enthusiastic surgical activity. Rather, the purpose of the report is to draw attention to a new hazard, disease or complication which has so far not been described, to put forward preliminary data on which a hypothesis may be based for subsequent testing, or on an occasional basis to reinforce a message of outstanding importance to anaesthetists, for example in respect of anaesthetic mortality.

In addition to the categories of Apparatus, Correspondence and Book Reviews, we shall publish the proceedings of the Anaesthetic Research Society three times per year, scientific hypotheses, historical articles and, wherever appropriate, reviews of the scientific content of professional meetings. All these changes result in an increase in the overall quantity of editorial material published in *British Journal of Anaesthesia*. In consequence we feel that it is sensible to allocate our issues to two rather than one volume per annum. This variation will occur in 1988 and should be accompanied also in the near future by the publication of a five-year cumulative index.

We hope that the changes described above will be met with approval by both our readers and potential authors. In addition, it is our intent that the health and reputation of this Journal will be maintained at the same high standard as that achieved by the distinguished line of anaesthetists who have served as previous Editors.

Graham Smith
(Editor)

Br. J. Anaesth. (1988), **60**, 3–9

HAEMODYNAMIC CHANGES DURING ANAESTHESIA INDUCED AND MAINTAINED WITH PROPOFOL

M. A. CLAEYS, E. GEPTS AND F. CAMU

SUMMARY

The haemodynamic effects of propofol, given as a single dose of 2 mg kg^{-1} immediately followed by a continuous infusion of 6 mg kg^{-1} h^{-1}, were studied in 10 elderly patients premedicated with lorazepam 1 mg i.v. All patients breathed room air spontaneously. Unconsciousness was successfully induced in all patients and persisted during the 60 min of the infusion. Statistically significant decreases in systolic and diastolic arterial pressures were observed 2 min after induction (28% and 19%, respectively) and during infusion (30% and 25%, respectively) and were related to decreases in systemic vascular resistance (21% following induction and 30% during infusion). Cardiac output was not affected at any time nor were stroke volume and heart rate. We conclude that the arterial hypotension associated with the induction and infusion of propofol is mainly a result of a decrease in afterload without compensatory increases in heart rate or cardiac output.

Propofol (2,6 diisopropylphenol) is a potent hypnotic currently formulated as an oil-in-water emulsion. Its pharmacokinetic profile suggested that anaesthesia could be induced and maintained by a continuous infusion of the drug [1–3]. Indeed, a number of groups have reported on the use of an infusion of propofol alone [4] or in combination with regional analgesia [5, 6], opioids [7, 8] or nitrous oxide [9–12].

In patients premedicated with morphine 0.15 mg kg^{-1} the surgical ED$_{50}$ for propofol given by constant infusion in association with 67% nitrous oxide was 54 µg kg^{-1} min^{-1} [13]. The reliable hypnotic activity of propofol suggests that it might be suitable as an alternative to nitrous oxide, etomidate or benzodiazepines for the maintenance of unconsciousness during analgesia-supplemented anaesthesia.

Although previous studies reported decreases in arterial pressures, no detailed studies of the cardiovascular and haemodynamic effects of the infusion of propofol alone in the absence of surgical stimulation are available. We have studied the haemodynamic effects of propofol administered as a 2-mg kg^{-1} bolus followed by a constant rate 6-mg kg^{-1} h^{-1} infusion exclusive of any other anaesthetic drug and in the absence of surgical stimulation.

PATIENTS AND METHODS

The study included 10 patients (ASA II, III; aged 50–75 yr) scheduled for total hip replacement without clinical evidence of cardiac or hepatic dysfunction. The demographic details of the study group are summarized in table I. Only one patient had a history of arterial hypertension. No other patients were in receipt of concurrent medication.

The study was approved by the University Ethical Committee and informed consent was obtained from each patient. All patients had received glycopyrrolate 0.4 mg i.m. 1 h before the study. A slow infusion of 5% glucose in lactated Ringer's solution was administered i.v. to replace insensible fluid loss and lorazepam 1 mg was

TABLE I. *Demographic data of patients (mean values ± SD)*

Age (yr)	62.4 ± 7.6
Weight (kg)	72.1 ± 14.7
Height (cm)	168.5 ± 4.9
Body surface (m^2)	1.82 ± 0.17

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Accepted for Publication: September 1, 1987.

injected i.v. as further premedication 40 min before the haemodynamic assessments.

Following the infiltration of local anaesthetic, a cannula (20 gauge) was inserted to the radial artery of the non-dominant arm to allow monitoring of arterial pressure, and a balloon-tipped thermodilution catheter (Edwards Laboratories) was placed in the pulmonary artery under continuous pressure control via the right internal jugular vein. ECG, heart rate, central venous pressure (CVP), systemic arterial and pulmonary artery pressures (systolic, diastolic and mean) were monitored continuously. All manipulations of the patient ended 20 min before baseline values were measured and any stimulation was avoided during the 60 min required for the haemodynamic evaluation. Following baseline measurements, unconsciousness was induced with propofol 2 mg kg^{-1} injected over 30 s. Simultaneously, a zero-order infusion of propofol was started at a rate of 6 mg kg^{-1} h^{-1} lasting 60 min and maintaining unconsciousness. All patients were allowed to breathe room air spontaneously. Special attention was paid to airway patency and the occurrence of apnoea and its duration; an oropharyngeal airway was inserted when needed. In seven patients arterial blood-gas analysis was performed before induction and after 45 min of infusion to evaluate blood-gas exchange.

Haemodynamic measurements were obtained before, and at 2, 6, 10, 15, 20, 30, 45 and 60 min after the initial administration of propofol and included determinations of heart rate, pulmonary artery pressures, pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), systolic (SAP) and diastolic (DAP) arterial pressures and cardiac output (CO). The pressure values were referenced to the level of the right

TABLE II. *Measured and calculated haemodynamic variables (mean ± SD). Differences from control*: $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$

	Time (min)				
	0	2	6	10	15
SAP (mm Hg)	136±17	99±22***	93±18***	94±18***	92±18***
DAP (mm Hg)	66±10	53±15**	50±12***	50±12***	48±10***
HR (beat min^{-1})	74±18	81±10	77±11	74±12	73±12
SPAP (mm Hg)	23±6	25±9	25±7	24±5	24±5
DPAP (mm Hg)	10±6	11±6	10±5	10±4	10±3
SVR (dyn s cm^{-5})	1070±265	846±300***	792±270***	767±232***	761±250***
PVR (dyn s cm^{-5})	76±38	103±61*	95±47*	85±45	86±39
CO (litre min^{-1})	6.6±1.0	6.1±1.0	6.3±1.0	6.4±0.7	6.4±0.8
SV (ml $beat^{-1}$)	93±26	77±17	83±17	88±17	90±18
CVP (mm Hg)	6.4±3.8	5.1±3.0	5.4±2.9	5.4±2.6	5.4±2.5
PCWP (mm Hg)	9.7±3.8	8.3±3.2	8.4±3.2	8.7±2.8	8.5±2.8
RPP (mm Hg beat min^{-1})	9945±2304	7880±1205*	7104±1035***	6866±1387***	6588±1393***
LVSW (g m $beat^{-1}$)	120±46	72±27***	76±27***	79±28***	78±26***
RVSW (g m $beat^{-1}$)	76±38	103±61*	95±47*	85±45	86±39
	20	30	45	60	
SAP (mm Hg)	93±17***	93±17***	96±16***	101±20***	
DAP (mm Hg)	48±10***	48±11***	50±10***	51±12***	
HR (beat min^{-1})	73±12	73±11	72±10	72±10	
SPAP (mm Hg)	23±5	23±5	23±4	24±4	
DPAP (mm Hg)	10±4	9±3	9±3	9±3	
SVR (dyn s cm^{-5})	776±220***	748±260***	748±272***	775±275***	
PVE (dyn s cm^{-5})	90±33	82±33	80±35	78±33	
CO (litre min^{-1})	6.4±0.9	6.5±1.0	6.7±1.2	6.5±1.1	
SV (ml $beat^{-1}$)	90±20	93±22	94±21	92±21	
CVP (mm Hg)	5.5±2.5	5.6±2.8	5.5±2.6	5.7±2.9	
PCWP (mm Hg)	8.6±3.1	8.5±2.7	8.3±2.9	8.6±3.0	
RPP (mm Hg beat min^{-1})	6732±1506***	6695±1501***	6896±1405***	7276±1633***	
LVSW (g m $beat^{-1}$)	79±28***	82±29***	85±16***	84±26***	
RVSW (g m $beat^{-1}$)	90±33	82±33	80±35	78±33	

atrium and recorded at end-expiration. Cardiac output (thermodilution) was determined in triplicate, using 10 ml of 5 % dextrose in water at room temperature, at the end-expiratory phase of the ventilatory cycle. A mean value was calculated. Derived cardiovascular variables obtained using standard formulae included stroke volume (SV), systemic vascular resistance (SVR), left and right ventricular stroke work (LVSW, RVSW), rate–pressure product (RPP) and pulmonary vascular resistance (PVR).

All data are reported as mean values ± SD. Statistical analysis of the haemodynamic measurements included Student's *t* test with Bonferroni correction.

RESULTS

The mean values of the measured and calculated haemodynamic variables are presented in table II.

Pulmonary artery pressures, heart rate, cardiac output, CVP and PCWP did not change significantly at any time. Systemic arterial pressures (SAP, DAP) decreased rapidly and to a significant extent, by 28 % and 19 %, respectively, following the bolus injection of propofol, and by 30 % and 25 %, respectively, during the maintenance infusion ($P < 0.001$). These changes were accompanied by significant decreases in SVR on induction (−22 %) and during infusion (−31 %) ($P < 0.001$). The RPP remained decreased during the whole period of the study ($P < 0.001$). PVR increased by 36 % ($P < 0.05$) immediately following the induction of unconsciousness, but was no more significantly affected during the infusion. SV decreased slightly 2 min after induction, and then returned gradually to baseline values. RVSW seemed unaffected, while LVSW decreased immediately by 39 % ($P < 0.001$), following the bolus injection of propofol and remained 30 % ($P < 0.001$) less than the control value during the infusion.

All 10 patients were helped by the placement of an oropharyngeal airway after induction, and in two patients its removal appeared necessary during the infusion period. Apnoea was noted in eight patients on induction of unconsciousness and lasted 90 ± 28 s (range 40–120 s). Arterial blood-gas analysis at 45 min indicated moderate respiratory impairment. pH values decreased from 7.38 ± 0.04 (control) to 7.30 ± 0.06 ($P < 0.01$) while Pa_{CO_2} increased from 5.07 ± 0.38 kPa (range 4.40–5.60 kPa) (control) to 5.66 ± 0.69 kPa (range 4.80–6.80 kPa) ($P < 0.01$).

DISCUSSION

The results of this study confirm the reported haemodynamic effects of an induction dose of propofol given as a single i.v. injection [9, 14–16] (table III) and are comparable to those found for other i.v. anaesthetics [17]. Apart from the initial tachycardia, similar changes were produced following the induction of anaesthesia with equipotent doses of thiopentone [16] and methohexitone [12].

During the maintenance of anaesthesia with an infusion of propofol (supplemented by nitrous oxide in oxygen) (table III), haemodynamic values similar to those obtained in the present study (except for the increase in HR) were observed, under comparable conditions, with Althesin [18], minaxolone [19], methohexitone [12, 20, 21] and thiopentone [22, 23].

Our results, obtained during the infusion of propofol in patients breathing room air, did not confirm the further decrease in arterial pressure and cardiac output reported by Prys-Roberts and colleagues [9], Coates and co-workers [14] and Monk and associates [15] (table III). These discrepancies can be explained to some extent by differences in methodology. The different haemodynamic response to propofol in the presence of nitrous oxide might be a result of the cardiovascular actions of the inhalation anaesthetic. Inhalation of a nitrous oxide–oxygen mixture produced a 15–20 % reduction of cardiac output [24] as a result of decreases in HR and contractility, and an increase in SVR.

As reported in previous studies, we observed no significant change in heart rate during induction with, or infusion of, propofol. Normally, arterial baroreceptors regulate arterial pressure by modifying heart rate and systemic vascular resistance. The change in HR induced by the decrease of arterial pressure is variably affected by different i.v. induction agents. Anaesthesia with i.v. infusion agents depresses baroreflex sensitivity and resets the heart rate reflex set point to allow a more rapid heart rate at lower arterial pressures [25, 26], or a slower heart rate despite decreased arterial pressures [27]. The infusion of propofol during nitrous oxide in oxygen anaesthesia appears to induce marked resetting of the heart rate baroreflex set point to allow lower arterial

TABLE III. *Extent of haemodynamic changes induced by propofol as reported in the literature. The changes are expressed as percent difference from baseline value.* **Statistically significant variations*

Authors/technique	HR	SAP	DAP	CO	SV	SVR	CVP	AWP	RPP	Premedication
Claeys (This study)										Lorazepam 1 mg i.v.
Bolus 2 mg kg^{-1}	+10%	−28%*	−19%*	− 7%	−17%	−21%*	−20%*	−14%	−22%*	Glycopyrrolate 0.4 mg i.m.
Inf. 6 mg kg^{-1} h^{-1}										
Spontaneous vent.,	− 2%	−30%*	−25%*	− 2%	− 1%	−30%*	−13%	−12%	−31%*	
no intubation,										
no N_2O										
Coates [14]										Morphine 150 μg kg^{-1} i.m.
Bolus 2 mg kg^{-1}	+ 2%	−28%*	−12%	−14%	−13%	−17%	− 9%	—	—	Atropine 10 μg kg^{-1} i.m.
Inf. 6 mg kg^{-1} h^{-1}										
Intubation, 67% N_2O	− 7%	−45%*	−35%*	−26%	−20%	−22%	−11%	—	—	
Spontaneous vent.										
Prys-Roberts [9]										Morphine 150 μg kg^{-1} i.m.
Bolus 1.5 mg kg^{-1}	=	−21%*	−16%	−12%	−12%	− 9%	—	—	−24%*	Atropine 10 μg kg^{-1}
Inf. 3 mg kg^{-1} h^{-1}										
Intubation, 67% N_2O	− 9%	−31%*	−28%*	−19%*	−11%*	−17%*	+66%*	—	−38%*	
Spontaneous vent.										
Monk [15]										Morphine 150 μg kg^{-1} i.m.
Bolus 2 mg kg^{-1}	=	−29%*	−22%*	−13%	−11%	− 6%	—	—	—	
Inf. 3.2–3.9 mg kg^{-1} h^{-1}										
Intubation, 67% N_2O	−14%	−47%*	−31%*	−31%*	−18%	−11%	—	—	—	
Spontaneous vent.										
Grounds [16]										Papaveretum 15–20 mg i.m.
Bolus 2.5 mg kg^{-1}	=	MAP: −32%		−12%*	−14%*	−21%*	− 9%	—	−29%*	Hyoscine 0.3–0.4 mg i.m.

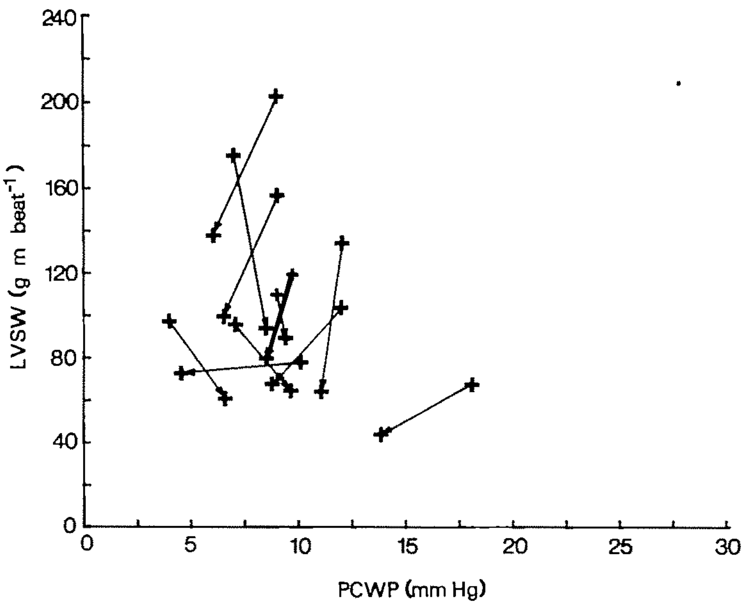

FIG. 1. Changes in left ventricular function during infusion of propofol. Arrows indicate changes between the measurement before propofol administration and the average value calculated from 10–60 min of propofol infusion for each patient. The thick arrow represents the mean for all patients.

pressures without tachycardia. Thus propofol may be regarded as exerting a central vagal predominance (or sympatholytic effect, or both).

In contrast to other i.v. anaesthetics, no depression of the baroreflex sensitivity was observed during the infusion of propofol (Prys-Roberts, personal communication, 1987). The baroreflex control of the SVR was markedly attenuated during the infusion and resetting of the reflex occurred to allow lower SVR for a given arterial pressure. The alteration of the baroreceptor reflexes suggests a direct vasodilating property of propofol on vascular smooth muscle, associated with a central depression of sympathetic outflow.

The absence of tachycardia with no significant decrease in CO is beneficial, since there is no increase in myocardial oxygen demand. The apparent absence of a myocardial depressant effect of the drug was confirmed by the maintenance of an adequate relation between LVSW and PCWP (fig. 1). Many have used RPP as an indirect index of myocardial oxygen demand [28]. In our study RPP decreased significantly after induction and during the infusion of propofol. However, the relevance of RPP is uncertain according to Reiz and colleagues [29] and Barash and co-workers [30].

The incidence and the duration of apnoea confirmed the greater ventilatory depressant effect of propofol observed by Grounds and colleagues [31] when compared with thiopentone. Dundee and co-workers [32] also reported more marked ventilatory depression in elderly patients. The significant increase in PVR at induction could result from hypoxic episodes during these apnoeic periods. During the infusion of propofol, the increase in Pa_{CO_2} confirmed the ventilatory impairment (see also references 9, 14, 15). Some cardiodepressive effects of propofol might have been masked in our study by the effects of the changes in Pa_{CO_2} on the cardiovascular system [33].

In conclusion, the major haemodynamic effect of propofol is a decrease in arterial pressure as a result of decreased SVR, rather than reduced SV or CO. In combination with other centrally vagotonic drugs, such as opioids, the resetting of the baroreflex set point may result in a slower HR and inadequate peripheral perfusion pressures, and has to be managed with care. The ventilatory impairment may limit the use of an infusion of propofol in spontaneously breathing patients.

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VECURONIUM INDUCED BRADYCARDIA FOLLOWING INDUCTION OF ANAESTHESIA WITH ETOMIDATE OR THIOPENTONE, WITH OR WITHOUT FENTANYL

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SUMMARY

To define the role of vecuronium in the occurrence of bradyarrhythmia, haemodynamic changes after the induction of anaesthesia were studied in 96 patients undergoing coronary artery bypass grafting. Patients were assigned to one of six groups according to different combinations of induction agents (etomidate 0.3 mg kg^{-1} or thiopentone 3 mg kg^{-1}, with fentanyl 0.003 mg kg^{-1}; etomidate 0.4–0.5 mg kg^{-1} or thiopentone 4–6 mg kg^{-1}, without fentanyl) and neuromuscular blocking drugs (vecuronium 0.112 mg kg^{-1}, pancuronium 0.112 mg kg^{-1} or suxamethonium 1 mg kg^{-1}). Anaesthesia was maintained with enflurane and nitrous oxide in oxygen. After initial diverse changes, heart rate decreased in all groups. Thirty minutes after intubation, the reduction of heart rate showed statistically significant differences between the different combinations of drugs: fentanyl–etomidate–vecuronium (group I) (the largest reduction) > etomidate–vecuronium (II) = fentanyl–thiopentone–vecuronium (IV) > thiopentone–vecuronium (V) = fentanyl–thiopentone–suxamethonium (VI) = fentanyl–etomidate–pancuronium (III). Five patients in group I, two in group IV and one each in groups II and V had a heart rate slower than 45 beat min^{-1}, whereas a similar value was never seen in groups III and VI. These results indicate that vecuronium has a bradycardic effect. This effect is more pronounced in association with etomidate than in association with thiopentone, and is augmented by the addition of fentanyl.

Anaesthetic drugs without deleterious cardiovascular effects are considered ideal, and are preferred in patients with poor cardiovascular reserve. Etomidate is gaining popularity in clinical anaesthesia, primarily because it has fewer cardiovascular effects compared with the barbiturates [1]. Vecuronium is often preferred to pancuronium because of its shorter duration of action and, importantly, because of its non-vagolytic effects [2]. Consequently, it has been routine in our clinic to induce anaesthesia in cardiac patients with etomidate preceded by a small dose of fentanyl, and to facilitate tracheal intubation with vecuronium.

Recently, reports have appeared which described asystole or severe bradyarrhythmia in connection with the use of vecuronium, when associated with severe vagal stimulation, or the administration of a large dose of opioid [3–8]. This was attributed to the non-vagolytic action, or the cardiovascularly "clean" effect of vecuronium. In addition, our own experience in cardiac anaesthesia suggests that vecuronium may, occasionally, cause severe bradyarrhythmia, even in association with minimal vagal stimulation, when it is combined with etomidate and a small dose of fentanyl [9]. Furthermore, some investigators have reported an increase in the requirement for atropine when vecuronium is used—even in the absence of vagal stimulation [10, 11].

Thus there are data which suggest that there may be an association between vecuronium and the occurrence of bradyarrhythmia. However, as yet, it has not been defined whether vecuronium is a primary causative agent or whether it acts merely as a cardiovascularly "clean" agent, such that the vagomimetic action of other drugs, or the bradyarrhythmic responses to vagal stimulation, appear unopposed. Furthermore, it is not known

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if, besides a large dose of opioid, a combination of any other agents predisposes to bradyarrhythmia when combined with vecuronium. Therefore, we designed the following study to clarify the role of vecuronium in the occurrence of bradyarrhythmia and the interactions of etomidate, thiopentone and a small dose of fentanyl with vecuronium.

PATIENTS AND METHODS

Once informed consent had been obtained, 96 patients (aged 38–72 yr) scheduled for coronary artery bypass grafting and classified as Montreal Heart Institute class 0 (normal risk [12]; exceptionally class I, if age over 65 yr was the only factor) were allocated to one of six groups according to the different combinations of induction agents (table I). Patients who had myocardial infarction within the last 3 months were excluded from the study. β-Adrenoceptor blocking drugs (acebutolol, atenolol, metoprolol or sotalol) were discontinued 24–72 h before surgery; other medication was continued until the day before the operation. Characteristics of the patients are summarized in table II.

Patients were premedicated with diazepam 10 mg by mouth and morphine sulphate 0.15 mg kg^{-1} i.m. approximately 1 h before the induction of anaesthesia. In the induction room a large-bore i.v. cannula and a radial artery catheter were inserted under local anaesthesia. Direct arterial pressure (Medex Novatrans MX800) and heart rate via ECG were monitored with a digital display (Siemens Sirecust).

Once the patients were observed to be in a stable condition, the induction of anaesthesia was started with a priming dose of vecuronium or pancuronium (except group VI). The priming dose was given to permit intubation sooner after induction, and timed to coincide with the maximum effects of etomidate or thiopentone. Patients in groups I, III and IV received fentanyl 2 min

TABLE I. *Combinations of induction agents and neuromuscular blocking drugs*

Group	Priming	Induction agents		Neuromuscular blocker
I ($n = 16$)	Vecuronium 0.012 mg kg^{-1}	Fentanyl 0.003 mg kg^{-1}	Etomidate 0.3 mg kg^{-1}	Vecuronium 0.1 mg kg^{-1}
II ($n = 16$)	Vecuronium 0.012 mg kg^{-1}	—	Etomidate 0.4–0.5 mg kg^{-1}	Vecuronium 0.1 mg kg^{-1}
III ($n = 16$)	Pancuronium 0.012 mg kg^{-1}	Fentanyl 0.003 mg kg^{-1}	Etomidate 0.3 mg kg^{-1}	Pancuronium 0.1 mg kg^{-1}
IV ($n = 16$)	Vecuronium 0.012 mg kg^{-1}	Fentanyl 0.003 mg kg^{-1}	Thiopentone 3 mg kg^{-1}	Vecuronium 0.1 mg kg^{-1}
V ($n = 16$)	Vecuronium 0.012 mg kg^{-1}	—	Thiopentone 4–6 mg kg^{-1}	Vecuronium 0.1 mg kg^{-1}
VI ($n = 16$)	—	Fentanyl 0.003 mg kg^{-1}	Thiopentone 3 mg kg^{-1}	Suxamethonium 1 mg kg^{-1}

TABLE II. *Characteristics of the patients studied*

	Group I	Group II	Group III	Group IV	Group V	Group VI
Male/female	15/1	14/2	14/2	14/2	16/0	12/4
Age (yr)	62±2.2	54±2.3	58±2.1	60±2.2	58±1.7	59±1.8
Weight (kg)	75±2.2	75±2.7	72±1.7	76±2.1	76±1.7	70±2.3
Number of diseased vessels						
3	8	10	10	11	9	8
2	7	5	6	3	6	8
1	1	1	0	2	1	0
Preoperative medication						
β-blocker	2	3	4	4	3	5
Digitalis	2	0	2	1	2	0

after the priming dose, were preoxygenated and 2 min later received etomidate or thiopentone. Patients in group VI received fentanyl and thiopentone as above, but without the pretreatment with a neuromuscular blocking drug.

In groups II and V, etomidate or thiopentone was administered 4 min after the priming dose. In the groups without pretreatment with fentanyl, the doses of etomidate and thiopentone were increased to attenuate the circulatory reactions to intubation. In this regard, the doses of both induction agents were comparable. Etomidate or thiopentone was injected slowly over 20 s via a rapidly running infusion of lactated-Ringer's solution. Following the injection of the etomidate or thiopentone, vecuronium, pancuronium or suxamethonium was administered. Commencing with the loss of consciousness, the lungs were ventilated via an anaesthetic face mask with 100 % oxygen, and up to 3 % inspiratory concentration of enflurane at the discretion of the anaesthetist.

Intubation of the trachea was performed 60 s after the injection of suxamethonium or at least 90 s after the injection of vecuronium or pancuronium. Arterial pressure and heart rate were recorded during the control, 2 min after the injection of fentanyl, 1 min after the injection of etomidate or thiopentone, and 2, 5, 10, 20 and 30 min after intubation of the trachea. Anaesthesia was maintained with enflurane and 50 % nitrous oxide in oxygen. Various concentrations of enflurane (0.4–3 %) were administered according to the value of the arterial pressure (systolic arterial pressure was to be kept between 90 and 130 mm Hg). Ventilation was adjusted to provide an end-expiratory carbon dioxide concentration of about 4.5 % measured by a capnograph (Datex Normocap).

Surgery was not started until 30 min after tracheal intubation; that is, there was no surgical stimulation during the observation period. If episodes of hypertension (systolic arterial pressure greater than 180 mm Hg) or tachycardia (more than 120 beat min^{-1}) developed in association with the induction of anaesthesia or the intubation of the trachea, and if additional doses of fentanyl or injections of nitroglycerin were required, the patient was excluded from the study. If the heart rate decreased to less than 45 beat min^{-1}, incremental doses of atropine 0.5 mg were given. In this situation, the heart rate before the injection of atropine (44 beat min^{-1}) was used also for the postinjection period in statistical analysis. If atropine was required before intubation of the trachea, the study was terminated.

The data are presented as mean ± SEM. The comparability of the groups before injections of drugs was assessed by analysis of variance. The statistical significance of the changes within each group was evaluated with the Student's t test for paired samples. The Student's t test for unpaired samples was used to compare the post-injection values between the groups. Differences were considered statistically significant when $P < 0.05$.

RESULTS

The six groups of patients were comparable in respect of age, weight and number of diseased coronary vessels (table II). There were no statistically significant differences in control heart rate or systolic arterial pressure (tables III, IV).

TABLE III. *Heart rate (beat min^{-1}) (mean ± SEM).* n = *16 for each group. ns = Not significant;* *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$

				Time after intubation (min)				
Group	Control	After fentanyl	1 min after induction	2	5	10	20	30
I	77 ± 3.0	73 ± 4.2 *	63 ± 3.5 ***	65 ± 3.6 ***	60 ± 2.8 ***	54 ± 2.6 ***	51 ± 2.1 ***	50 ± 1.6 ***
II	77 ± 3.2	—	68 ± 1.9 **	75 ± 2.4 ns	69 ± 2.4 *	62 ± 2.1 ***	57 ± 2.0 ***	53 ± 1.6 ***
III	78 ± 4.2	80 ± 4.8 ns	77 ± 3.7 ns	81 ± 4.2 ns	77 ± 4.1 ns	72 ± 3.9 ns	70 ± 3.5 **	67 ± 3.2 ***
IV	78 ± 2.9	72 ± 2.8 **	78 ± 2.3 ns	74 ± 2.7 *	67 ± 2.3 ***	59 ± 2.1 ***	58 ± 1.9 ***	56 ± 1.9 ***
V	73 ± 3.6	—	82 ± 3.8 **	81 ± 3.9 **	75 ± 3.4 ns	66 ± 3.1 **	62 ± 2.6 **	58 ± 2.2 ***
VI	74 ± 4.0	72 ± 4.6 ns	79 ± 3.5 ns	75 ± 3.8 ns	66 ± 3.1 **	62 ± 2.6 ***	60 ± 2.4 ***	60 ± 2.2 ***

TABLE IV. *Systolic arterial pressure (mm Hg) (mean ± SEM).* n = *16 for each group. ns = Not significant;* *P < *0.05;* **P < *0.01;* ***P < *0.001*

Group	Control	After fentanyl	1 min after induction	Time after intubation (min) 2	5	10	20	30
I	143±4.3	141±4.4 ns	117±3.9 ***	129±3.2 **	128±3.3 **	121±3.7 ***	112±3.2 ***	115±2.7 ***
II	141±3.5	—	123±5.1 ***	124±3.1 ***	127±3.6 **	115±3.1 ***	112±2.0 ***	111±2.7 ***
III	138±5.1	138±4.9 ns	116±4.5 ***	126±4.7 **	124±4.3 *	115±3.1 ***	113±2.5 ***	112±1.9 ***
IV	140±3.3	141±4.8 ns	117±4.6 ***	126±6.2 *	116±3.9 ***	104±3.1 ***	101±2.5 ***	104±2.4 ***
V	142±3.2	—	128±5.2 *	121±3.4 ***	113±3.5 ***	108±2.8 ***	99±1.7 ***	99±3.0 ***
VI	134±2.6	131±3.8 ns	109±9.0 ***	120±4.7 **	110±3.2 ***	101±2.3 ***	99±2.3 ***	104±3.0 ***

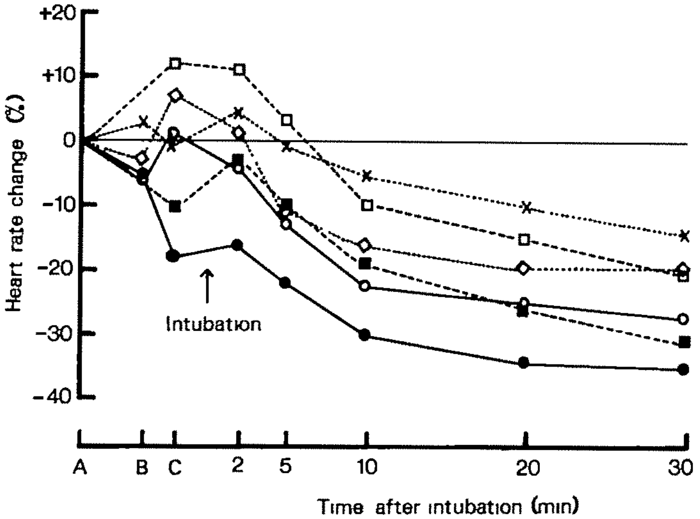

FIG. 1. Time course of heart rate changes in the six groups. Changes are expressed as mean percent reduction from the control (n = 16 for each group). A = Control; B = 2 min after fentanyl; C = 1 min after induction; thereafter, time after intubation. ●——● = Group I; ■——■ = group II; x...x = group III; ○——○ = group IV; □——□ group V; ◇...◇ = group VI.

After initial and varied changes in heart rate caused by the induction of anaesthesia and the subsequent intubation of the trachea, heart rate decreased in all groups, but to different degrees (fig. 1, table III). It is noteworthy that the heart rate was lowest in group I during the entire course of the study. In actual fact, mean heart rate would have been even less if atropine had not been given to these patients. In five out of 16 patients in group I, heart rate decreased to less than 45 beat min^{-1} between 5 and 30 min after intubation, and incremental doses of atropine were injected. In other groups, atropine was given sparingly but two patients in group IV, and one each in groups II and V received atropine 0.5–1.5 mg (mean 0.78 mg). In contrast, no patient in groups III and VI received atropine. We could not find any causal relation between the injection of atropine and preoperative medications. Of the 96 patients studied, 21 were receiving β-adrenoceptor blocker in the preoperative period (discontinued 24–72 h before surgery) and seven were receiving digitalis. Only two out of nine patients who received atropine had been receiving β-blocker and one out of nine was receiving digitalis. The injection of atropine frequently caused a junctional rhythm: in three patients in group I and all patients in groups II and IV, junctional rhythm, which

TABLE V. *Decreases in heart rate at 30 min after tracheal intubation (% reduction from control) and comparison between two groups at a time. ns = Not significant,* $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$

	Group I	Group II	Group IV	Group V	Group VI	Group III
Decrease (%)	35.9±1.7	29.1±2.3	27.4±2.2	20.4±2.4	18.1±2.6	12.4±3.6
Group I	—	*	**	***	***	***
Group II	—	—	ns	*	**	***
Group IV	—	—	—	*	*	**
Group V	—	—	—	—	ns	ns
Group VI	—	—	—	—	—	ns

lasted 5–15 min, developed immediately after the injection.

Although the degree of the change was different, the heart rate in each group reached its lowest value between 20 and 30 min after intubation. Therefore, the differences in the changes of heart rate between the groups were compared 30 min after intubation (table V). Heart rate decreased to different extents in association with the different combinations of drugs: fentanyl–etomidate–vecuronium (group I) (the largest reduction) > etomidate–vecuronium (II) = fentanyl–thiopentone–vecuronium (IV) > thiopentone–vecuronium (V) = fentanyl–thiopentone–suxamethonium (VI) = fentanyl–etomidate–pancuronium (III).

The following comparisons are of particular interest:

(1) The reduction in heart rate in group IV was greater than that in group VI; that is, because suxamethonium only has a brief period of action, vecuronium itself has a bradycardic effect.

(2) The reduction in heart rate in group I was greater than that in group IV. The same applies to groups II and V. This means that bradycardia associated with the use of vecuronium was more pronounced when etomidate, as compared with thiopentone, was used.

This comparison also showed, as expected, that the addition of fentanyl decreased heart rate—as seen in the difference of heart rate responses between groups I and II as well as between groups IV and V. As the large difference in the decrease in heart rate between groups I and III shows, the substitution of pancuronium for vecuronium attenuated greatly the decrease in heart rate.

In contrast to the varied changes in heart rate, changes in systolic arterial pressure were similar in all groups. There were no statistically significant differences between the groups (table IV).

Three patients were excluded from the analysis. Two patients who had relatively high initial heart rates (93 and 98 beat min^{-1}) developed tachycardia and hypertension before intubation after having received thiopentone and vecuronium (group V) and required the administration of fentanyl and nitroglycerin. One patient in group I was given atropine 0.5 mg before intubation because of a decrease in heart rate.

DISCUSSION

The induction of anaesthesia with different combinations of drugs caused different patterns and degrees of change in heart rate, whereas the patterns and degrees of change in arterial pressure were similar.

The combination of etomidate, vecuronium and a small dose of fentanyl led to the slowest heart rate. When thiopentone was substituted for etomidate, or when pancuronium was used instead of vecuronium, the decrease in heart rate was significantly less.

The vagomimetic effects of fentanyl [13] and the vagolytic [14] and sympathomimetic [15, 16] effects of pancuronium are well established. Therefore, the bradycardic effect of fentanyl and the bradycardia-attenuating effect of pancuronium, which we demonstrated here, were not unexpected. In our view the present study demonstrates that vecuronium has a bradycardic effect, and that this effect is more pronounced when vecuronium is administered along with etomidate than when it is given in association with thiopentone.

To reach this conclusion, we compared the patients receiving fentanyl, thiopentone and vecuronium (group IV) with those receiving fentanyl, thiopentone and suxamethonium (group VI), because group VI constitutes a control for group IV as a result of the brief action of suxamethonium. At present we have no explanation for the mechanism of the observed bradycardic effect of vecuronium. Nor are there experimental data which confirm this observation. Obviously, it would have been of interest to compare the haemodynamic effects of vecuronium and suxamethonium in patients receiving etomidate and fentanyl. However, we chose thiopentone as an induction agent because we had noted previously several cases of severe bradycardia and asystole after a single injection of suxamethonium, when combined with etomidate and a small dose of fentanyl [17]. As a result, we considered the inclusion of this combination to be unjustifiable.

In many of the previous studies in which bradycardia was documented after the injection of vecuronium, a large dose of fentanyl or sufentanil had been used for the maintenance of anaesthesia [10, 18]. Clinically insignificant decreases in heart rate were reported when vecuronium was used along with thiopentone or with thiopentone and a small dose of fentanyl [19, 20]. However, in contrast, no changes in heart rate or in haemodynamic stability have been recorded after the injection of vecuronium with or without the concomitant use of fentanyl [21–25].

In those studies in which there were only minor or no changes in heart rate, the haemodynamic responses were studied for up to between a few minutes and 10 min after the injection of vecuronium. As the development of the changes in heart rate in the present study shows, the decrease in heart rate became evident only at least 10 min after intubation (see the difference in the changes in heart rate between groups IV and VI (fig. 1): significant difference starting at 10 min). Moreover, occasional episodes of asystole or severe bradycardia have been reported to occur about 20 min after the injection of vecuronium [3, 5, 26]. Therefore, it is possible that the bradycardic effect of vecuronium does not always become evident immediately after the injection. More importantly, however, the type of induction agent plays an important role in the differences between the heart rate responses. In the present study, the use of etomidate led to more pronounced bradycardia than the use of thiopentone. On occasions, we observed marked bradycardia or asystole during induction in response to vagal stimulation, and when vecuronium was combined with etomidate and a small dose of fentanyl. This kind of arrhythmia was never observed when thiopentone or methohexitone was used instead of etomidate [9]. Similarly, etomidate does not protect against bradyarrhythmias induced by a second injection of suxamethonium, although thiopentone does [27]. Furthermore, the first injection of suxamethonium caused bradyarrhythmia relatively frequently in adult patients when etomidate and a small dose of fentanyl were used for the induction of anaesthesia [17].

The mechanism for these different responses in heart rate with either etomidate or thiopentone may be explained by the different actions of etomidate and barbiturates on vagal activity. In animal studies, etomidate was shown either to have minimal effects on vagal activity or, on occasions, to enhance it, whereas methohexitone was shown to inhibit vagal activity and cause a tachycardia [28]. Thus barbiturates seem to protect against vagal stimulation, whereas etomidate does not.

Although thiopentone has been used as a sole agent for the induction of anaesthesia in patients with coronary artery disease [29, 30], our experience with thiopentone as a sole agent was not satisfactory. We saw two cases of tachycardia and hypertension before intubation and immediately after the injection of thiopentone. The common feature in both patients was a relatively high heart rate before induction, which might indicate inadequate premedication. Such patients may show a response to thiopentone quite different from that of normal well-sedated patients in whom thiopentone causes a decrease in arterial pressure as a result of its inhibitory action on sympathetic activity [31, 32].

A problem arises with the attempt to treat bradycardia with atropine because, as we found, a junctional rhythm develops fairly often [11]. This finding is not too surprising; in moderate doses (0.4–1.2 mg i.v.), atropine may cause junctional rhythm, A–V dissociation and ventricular arrhythmia [33–35]. In a larger dose (3 mg i.v.), the occurrence of arrhythmia was reported to be rare [36]. It was postulated that atropine inhibits the influence of the vagus on the A–V node before the sinus node [33]. In this situation, the A–V node can escape and establish itself as the pacemaker. Therefore, it can be argued that this imbalance in the effects of atropine may become more marked in a situation in which the heart rate has been decreased markedly by strong vagal stimulation. This may explain the frequent occurrence of junctional rhythm in the present study. Interestingly, when atropine 0.5 mg i.v. is administered at the time of induction, a junctional rhythm follows only rarely and the occurrence of bradycardia is prevented (unpublished observation).

Enflurane, which was used as a maintenance anaesthetic, is not devoid of chronotropic effects. It may increase or decrease heart rate depending on the initial heart rate [37–39]. If a patient's heart rate while awake is high, heart rate tends to decrease, and *vice versa*. In the present study the induction of anaesthesia caused, after the initial varied changes, a decrease in heart rate in all groups—even in those in which fentanyl was not administered. Anaesthesia probably abolished preanaesthetic excitement and led to the decrease in heart rate. Unfortunately, it was not possible for us to administer the same concentration of enflurane to all patients. However, because different concentrations resulted mainly from the fact that fentanyl was or was not used for induction, comparisons between the groups with fentanyl-pretreatment or between the groups without fentanyl can be considered to be valid even in the presence of enflurane.

β-Adrenoceptor blocking drugs were discontinued 24–72 h before surgery in the present study. However, since the cardiovascular effects of a short-acting β-adrenoceptor blocker, propranolol, have been shown to persist for 72 h after discontinuation [40], one may ask whether the preoperative use of β-adrenoceptor blockers influenced our results. As the number of patients who were receiving β-blockers and required the injection of atropine shows, the preoperative use of β-blocker did not appear to modify the changes in heart rate.

In conclusion, our results indicate that vecuronium has a bradycardic effect, and that this effect is pronounced in combination with etomidate and a small dose of fentanyl. When thiopentone is substituted for etomidate or pancuronium is used instead of vecuronium, the decrease in heart rate is attenuated.

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COMPARISON OF SEDATION WITH TEMAZEPAM BY MOUTH AND DIAZEMULS I.V. FOR DENTAL SURGERY

Variability in Absorption may Influence Clinical Effect

H. E. HOSIE, I. M. BROOK AND W. S. NIMMO

SUMMARY

Temazepam elixir 30 mg by mouth was compared with i.v. Diazemuls titrated to a maximum dose of 20 mg in a double-blind study of 50 patients undergoing elective minor oral surgery. The treatments produced a similar reduction in anxiety score and similar degrees of patient relaxation and co-operation. The diazepam group had greater amnesia during surgery, but also showed significant slowing of reaction time at the time of discharge. Patients given temazepam elixir showed wide variations in plasma concentrations. Patients with low plasma temazepam concentrations at the time of surgery showed no significant reduction in anxiety scores.

Sedation, coupled with local anaesthesia, has been advocated as a safe alternative to general anaesthesia for dental surgery.The advantages of such a regimen are its minimal effects on vital signs, protective reflexes and patient co-operation, the minimal requirement for monitoring and rapid recovery to street fitness [1]. Sedatives administered by mouth can be as effective as those given i.v. and have the advantages of greater patient acceptability, ease of administration, safety and fewer sequelae [2, 3].

Temazepam, a safe and commonly-used benzodiazepine with a short duration of action and no active metabolites, has been reformulated as an elixir which is thought to be more rapidly absorbed than the original gelatin capsules. Significantly greater plasma concentrations of temazepam are found 20 min after the oral administration of the elixir when compared with the capsules [4].

We have compared temazepam elixir administered by mouth with i.v. Diazemuls in patients undergoing minor oral surgery and attempted to relate the plasma concentrations of temazepam with effect. The clinical effectiveness of temazepam by mouth has been reported elsewhere [5], and temazepam was shown to have a lesser amnesic effect than diazepam as judged by recall of operative events and picture cards. Reaction times on discharge 45 min after operation were shown to be significantly increased following the administration of diazepam when compared with pre-administration values. No significant changes in reaction times were demonstrated in the temazepam group [5].

PATIENTS AND METHODS

Fifty patients (ASA grade I) undergoing elective minor oral surgery and requesting sedation, gave written informed consent to take part in the study, which had local Ethical Committee approval. Patients already taking benzodiazepine preparations were excluded. On arrival, 1 h before surgery was expected, patients were allocated randomly to two groups. Group I received temazepam 30 mg in 15 ml of elixir by mouth and those in group II received placebo elixir 15 ml. Fifty minutes after taking the elixir, patients were transferred to the dental chair and those in group I were given an i.v. injection of Intralipid 4 ml (as placebo); those in group II received i.v. Diazemuls over 2 min to a maximum of 20 mg titrated to slurring of speech or ptosis. Both patient and dentist were unaware of the sedation used. The dentist performed the surgery under

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local anaesthesia. Arterial pressure and heart rate were recorded using a Sears automatic digital sphygmomanometer on five occasions during the study: before taking the elixir; 45 min after the elixir but before transfer to the dental chair; after the i.v. injection and local block but before starting surgery; at completion of surgery and, finally, before discharge (normally 45 min after completion of surgery). Rate–pressure product was calculated by multiplying systolic arterial pressure by heart rate to provide an index of sympathetic activity.

Eleven patients re-attended for extraction of impacted third molars on the opposite side and were given the alternative sedation on their second visit, although both patient and dentist remained unaware of the sedation used. Data obtained from these patients were analysed separately.

Assessments

The type of surgery and its duration were noted. The dentist assessed the degree of difficulty of surgery as easy (a procedure involving raising a flap and elevating the tooth), moderate (where bone removal or sectioning the tooth was required) or difficult (where there was particular surgical difficulty). In addition he graded patient co-operation as excellent (relaxed), satisfactory (surgery completed) or unsatisfactory (surgery abandoned).

Anxiolysis was assessed using a 100-mm visual linear analogue scale (VAS) with anxiety/apprehension and relaxed/confident being the end-points and measurement from the "relaxed" end. The VAS was completed by the patient before any sedation was given, after surgery and on follow-up at 1 week.

Amnesia was assessed by testing the patients' recall of perioperative events. These included the administration of the local anaesthetic, the accurate recall of three picture cards shown to the patient during surgery and the ability to remember the number of times the heart rate and arterial pressure had been measured during the study.

Reaction times were measured using a BBC computer and a VDU. The response time between the presentation of a random audible and visual signal and pressing a button was measured electronically. After initial familiarization with the equipment 10 measurements were made on each of three occasions: before sedation, before surgery 45 min after taking the elixir and before discharge. The mean reaction time on each occasion was calculated.

Blood samples were taken during surgery and before going home, and plasma concentrations of temazepam were measured by high performance liquid chromatography. The chromatography consisted of a Model 302 pump (Gilson, Villiers le Bel, France) fitted to a Holochrome variable-wavelength ultraviolet detector (Gilson) operated at a maximum sensitivity of 0.02 a.u.f.s. and connected to a C-R1B chromatopac integrator (Shimadzu Corporation, Kyoto, Japan). Injection was made by syringe via a Rheodyne valve, Model 7125, with 20-µl loop (Rheodyne, CA, U.S.A.). The column was 150 × 4.6 i.d. and prepacked with 5-µm Microsorb C18 (Rainin Instrument Co. Inc. U.S.A.). Chromatography was performed in reverse-phase mode using a solvent system of methanol–water–acetonitrile (40:50:10 v/v) at a flow-rate of 1.5 ml min^{-1} and the column effluent was monitored at 230 nm. The chromatograph was operated at 2200 p.s.i. and room temperature.

Reagents were of analytical grade and all inorganic reagents were prepared in freshly glass-distilled water. Chloroform was Distol grade, methanol and acetonitrile were HPLC grade (Fisons, Loughborough, U.K.). Borate buffer 0.2 mol litre^{-1} containing sodium hydroxide 1 mol litre^{-1} was adjusted to pH 9.4 with sodium hydroxide solution 0.1 mol litre^{-1}. A standard solution of temazepam was prepared in distilled water at a concentration of 10 µg ml^{-1} and carbamezepine (the internal standard) at 20 µg ml^{-1}. Temazepam was supplied by Wyeth Laboratories and carbamezepine by Sigma Chemical Co. Ltd.

Plasma samples (0.5 ml) were spiked with internal standard (150 ng) and vortex-mixed with borate buffer 1.0 ml for 5–10 s. This mixture was extracted by shaking it with chloroform 4.0 ml for 15 min on an Orbital mixer, Model R100/TW (Luckham Ltd, Sussex, U.K.). After centrifugation (3000 rev min^{-1}) for 5 min the chloroform layer was transferred to a tapered test-tube and evaporated to dryness under a stream of oxygen-free nitrogen. The residue was re-dissolved in mobile phase (60 µl) and a 20-µl portion was injected to the chromatograph. Standard dilutions containing temazepam 500 ng ml^{-1} in drug-free plasma were prepared as above for calibration.

Statistical analyses were performed using Student's t test and Chi-squared analyses.

RESULTS

The two groups of patients did not differ significantly with respect to age, weight, sex distribution or in the time taken for surgery (table I). Most of the surgical procedures were extraction of impacted third molars, but included apicectomies and surgical removal of roots. The degree of difficulty of surgery did not differ significantly between the groups. The mean dose of i.v. diazepam was 16.6 mg. All procedures were completed, with co-operation being classified as excellent in the majority of the patients; there were no significant differences between the groups in this regard.

Plasma concentrations of benzodiazepines

Blood samples for assay of temazepam concentrations were obtained from 24 patients. One patient had an inadequate sample at the time of surgery and three samples taken at time of discharge home were insufficient for assay (fig. 1). Plasma concentrations of temazepam at the time of surgery (45 min after the elixir) varied widely—from 115 ng ml^{-1} to 780 ng ml^{-1}. Concentrations at the time of discharge home (90–135 min after the elixir) were less variable. Plasma concentrations at the time of surgery were less than 200 ng ml^{-1} in seven of the 23 patients. Subsequently, six of these individuals achieved concentrations similar to the other patients at 2 h. It would appear that these patients had delayed absorption of the elixir and that, at the time of surgery, plasma concentrations were low. Therefore, in addition to a comparison of the groups receiving diazepam and temazepam, the data from these seven individuals were analysed separately.

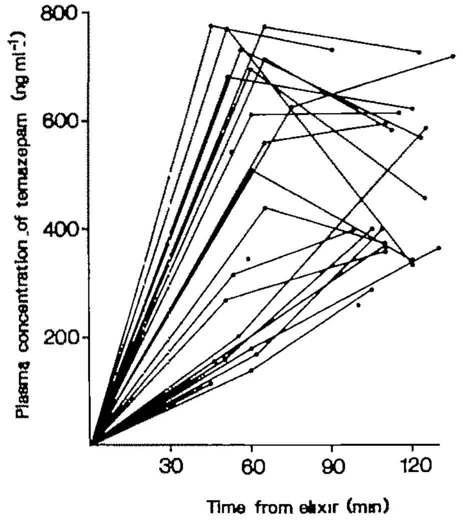

FIG. 1. Plasma concentrations of temazepam following oral administration of elixir.

Both groups had similar anxiety scores before taking the elixir. Patients given diazepam and those with high plasma temazepam concentrations showed a significant decrease in anxiety score which persisted 1 week later at review (fig. 2). Patients with low plasma concentrations of temazepam had lower initial anxiety scores and showed no significant change at any time.

Rate–pressure product (RPP) was used as an index of sympathetic activity and an indirect estimation of anxiolysis (fig. 3). Before random allocation to groups, those who subsequently received temazepam had a significantly lower RPP ($P < 0.05$); thereafter, these patients showed a significant increase in RPP at the time of surgery compared with initial values ($P < 0.05$), with RPP decreasing on completion of surgery and then decreasing further before discharge. Those with low temazepam concentrations showed the same pattern of changes, but higher values. Patients given i.v. Diazemuls showed a different pattern, with no increase in RPP at the time of surgery and a significant reduction in RPP before being allowed home compared with pretreatment values ($P < 0.01$).

TABLE I. *Sex distribution, age and weight of patients (mean (range)), mean (SEM) dose of sedative and mean (range) duration of surgery*

	M	F	Age (yr)	Weight (kg)	Dose (mg)	Time taken (min)*
Temazepam elixir (*n* = 25)	5	20	24.2 (16–51)	65.5 (45–91)	30	12.5 (2–30)
Diazepam i.v. (*n* = 25)	5	20	26.2 (17–50)	65.3 (45–105)	16.6 (0.6)	14.5 (1–30)

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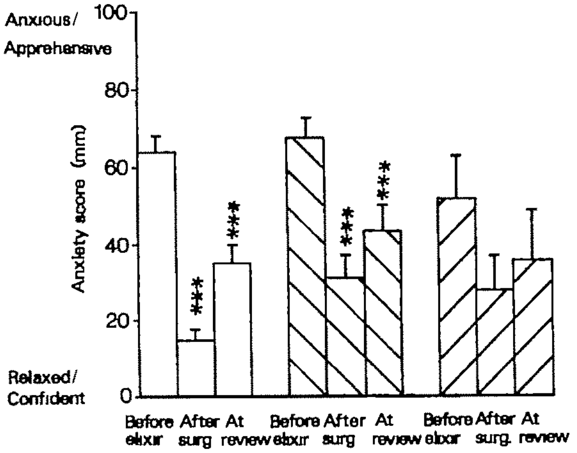

FIG. 2. Mean anxiety scores (±SEM) before sedation, after surgery and at follow-up. $***P < 0.005$. □ = Diazepam; ▧ = temazepam, high concentration; ▨ = temazepam, low concentration.

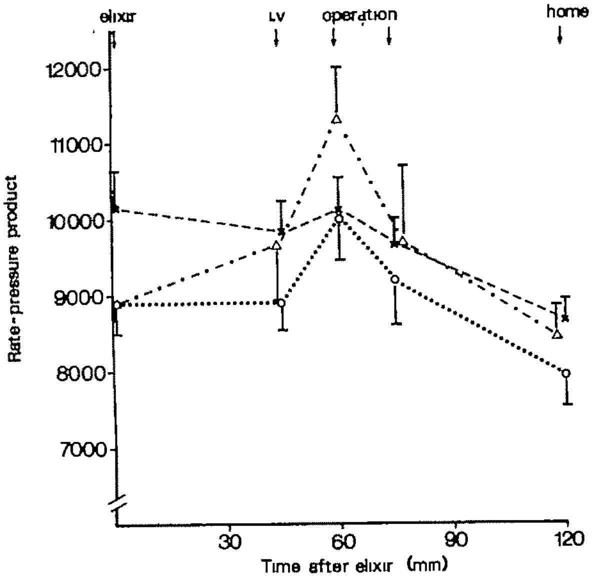

FIG. 3. Mean RPP (±SEM) at intervals after elixir. x = Diazepam; ○ = temazepam, high concentration; △ = temazepam, low concentration.

Paired data

The degree of difficulty of the procedure and patient co-operation were similar at both visits. Seven of the patients received temazepam elixir at their first visit and diazepam i.v. at the second operation.

Anxiety scores in those attending for surgery on the second occasion were significantly lower than their initial anxiety scores, and were similar to those found following the first postoperative review. A further small but insignificant reduction in anxiety score was seen subsequent to the second procedure (fig. 4). At the first operation the RPP showed a significant increase at the time of surgery with a decrease to pre-operative values during recovery, but during the second operation RPP remained virtually unchanged (fig. 5).

At review, following the second procedure, patients were asked which sedation they preferred. Eight of the 11 preferred diazepam, two temazepam and one was happy with either. Four patients preferred the first sedative and six preferred the sedation given on the second occasion. The differences were not significant.

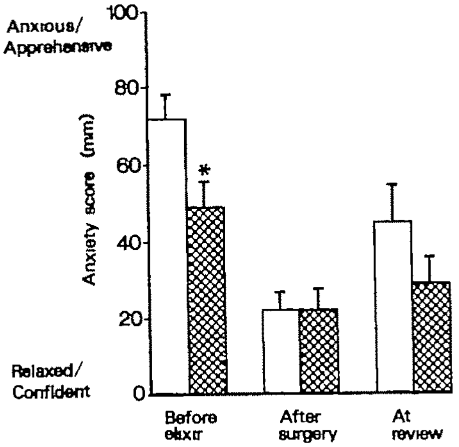

FIG. 4. Mean anxiety scores (±SEM) in 11 patients attending for two procedures. Open columns = first procedure; cross-hatched columns = second procedure. $*P < 0.05$.

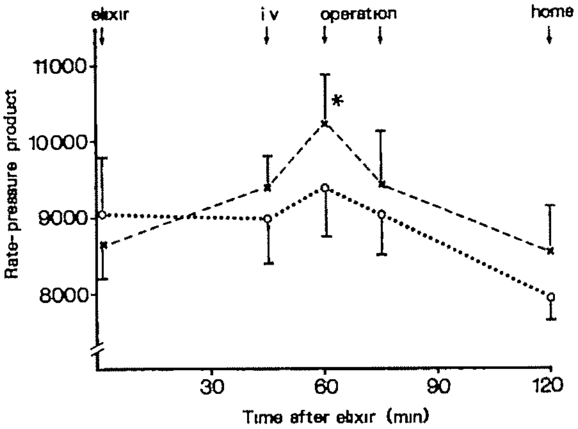

FIG. 5. Mean RPP (±SEM) after elixir in patients attending for two procedures. x = First procedure; ○ = second procedure. $*P < 0.05$.

DISCUSSION

We have previously reported that a fixed dose of temazepam elixir administered by mouth in patients undergoing minor oral surgery is acceptable as a sedative agent to both patient and dentist [5]. Our finding that temazepam elixir 30 mg is comparable to a mean dose of Diazemuls 16.6 mg i.v. agrees with work of Douglas and colleagues [2] who found that temazepam 20 mg in gelatin capsule formulation 1 h before operation was comparable to a mean dose of diazepam 12 mg in propylene glycol in patients having endoscopy. O'Boyle, Harris and Barry [3] compared temazepam 40 mg in capsule formulation with a maximum of Diazemuls 10 mg i.v. in minor oral surgery. In their study, surgery started 40 min after the oral administration of the capsules and plasma concentrations were not measured. A bioavailability study by Pickup, Rogers and Launchbury [4], comparing temazepam in capsules with the elixir, showed that higher plasma concentrations were reached 20 min after the elixir and suggested that a more rapid onset of activity was possible using the elixir. It may be that the discrepancy in comparability between these studies is attributable to a combination of the different drug formulations and the timing of surgery.

It is of interest that seven out of 23 patients given temazepam elixir had plasma concentrations less than 200 ng ml^{-1} at the time of surgery. All patients were ASA grade I and were not receiving drugs or other medications. There was no history of any gastrointestinal disease that would delay gastric emptying. Although patients had not been instructed to fast before surgery, on direct questioning it appeared that some had fasted for several hours, whereas others had had a light meal within the previous 4 h. However, there was no correlation between fasting and non-fasting patients and plasma concentrations of temazepam. Similarly, there was no correlation between age, sex or weight and plasma temazepam concentration at the time of surgery.

A number of factors can affect drug absorption, including the formulation of the drug and the degree of anxiety experienced by the patient. Nakano, Ogawa and Kawazu [6] found that a high neuroticism score was associated with higher plasma diazepam concentrations and suggested that an increase in anxiety was associated with more rapid absorption of benzodiazepines. Our patients with low plasma temazepam concentrations at the time of surgery did not differ significantly from the other patients in terms of anxiety score, although their initial score was lower and numbers are small. Patients given temazepam had a lower rate–pressure product than those given diazepam. The correlation coefficient between anxiety score before treatment and temazepam concentration was poor ($r = 0.0754$).

Attempts have been made to relate plasma concentrations of benzodiazepines with effect. However, Nakano, Ogawa and Kawazu [6] found poor correlation coefficients between sedation—as measured using Choice Reaction Time Test—and plasma diazepam concentrations after diazepam by mouth. In the seven patients with low temazepam concentrations at the time of surgery, the decrease in anxiety score following surgery was not significant and they showed a marked increase in rate–pressure product at that time—although, once again, the difference was not significant. Despite the numbers being small it may be that plasma concentrations greater than 200 ng ml^{-1} are associated with more marked anxiolysis.

Bioavailability studies by Fucella [7] in four fit volunteers suggested that peak plasma concentrations were achieved 20–40 min after the administration of temazepam by mouth in solution and in soft gelatin capsules. However, in the study by Pickup and co-workers [4] in 10 fit volunteers, peak plasma concentrations were reached after 95 min for both elixir and capsules. From our study of 25 fit patients awaiting surgery we find plasma concentrations less variable at the second sample 90–135 min after the elixir. If the effects of sedation and anxiolysis are related to the plasma concentration of the drug, then increased effects may be seen if surgery takes place at a time when peak plasma concentrations could be anticipated.

Comparing temazepam and diazepam overall, our findings support the findings of previous studies. Both drugs reduce anxiety and provide satisfactory conditions for the surgeon and the patient. We have previously reported the lack of amnesic effect of temazepam. The flattened rate–pressure product graph (fig. 3) suggests that i.v. diazepam may obtund the sympathetic response to surgery, whereas temazepam may only reduce it. Although more patients receiving both sedatives expressed a preference for diazepam, this may have been related to the order of administration of the sedation. Both sedatives reduced anxiety to similar values for repeat procedures. The "paired patients" in our sample had lower anxiety scores at their second presentation and these scores correlated well with their scores after the first procedure. This could be attributed to the good effect of the sedative previously given, or simply to having experienced the surgery before.

Anxiety scores did decrease at the second visit, but not to any significant extent. During the first visit the rate–pressure product showed a significant increase at the time of surgery, whereas at the second operation there was no change throughout the study. However, seven of the 11 patients had been given temazepam at the first visit and diazepam at the second, and this could account for the differences seen.

Temazepam is a drug with a good record of safety and efficacy. Certainly, the oral route of administration has many factors to commend it, especially to those not proficient in i.v. cannulation and to patients who do not wish injections or residual effects. However, it would appear that further investigation is merited of the absorption of temazepam in patients about to undergo surgery.

ACKNOWLEDGEMENTS

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PREGNANCY DELAYS PARACETAMOL ABSORPTION AND GASTRIC EMPTYING IN PATIENTS UNDERGOING SURGERY

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SUMMARY

Gastric emptying may be delayed during pregnancy by hormonally mediated relaxation of the musculature of the stomach and by mechanical effects. In the present study, the rate of paracetamol absorption was used to measure gastric emptying in 14 non-pregnant women undergoing minor gynaecological surgery, and in 28 women undergoing termination of pregnancy. Of the pregnant patients 16 were of 8–11 weeks gestation and 12 were of 12–14 weeks gestation. Paracetamol absorption was delayed in those who were 12–14 weeks pregnant compared with non-pregnant controls. Paracetamol absorption in the 8–11 weeks pregnant group was between the other two groups, but was not significantly different from either.

Nausea, vomiting and heartburn occur during early pregnancy, and may indicate abnormal gastrointestinal function at this time. An increase in the release of progesterone from the corpus luteum and placenta causes relaxation of gastrointestinal smooth muscle and this may result in a decrease in the motility of the stomach [1]. Gastric emptying may also be impeded mechanically during pregnancy if the stomach is pushed into a more horizontal position and the pylorus is displaced upwards and posteriorly [2].

Previous studies of gastric emptying during pregnancy have produced conflicting results. In 1937, Hansen [3] found that the emptying time of a radio-opaque test meal was increased by 30–90 min during pregancy. However Boyden and Rigler [4], using fluoroscopic examination, found little alteration in gastric emptying during the second and third trimester of pregnancy, but suggested that peristalsis may have been slower. Hunt and Murray [5] used dye dilution to measure the rate of emptying of 750 ml of fluid in five pregnant women and showed that it did not differ from that found in the same patients 40 weeks after delivery. In 1970, Davison, Davison and Hay [6] measured gastric emptying using a double sampling dye-dilution technique in 11 non-pregnant women and 11 women of at least 34 weeks gestation. The mean total emptying time of a water test meal was increased in pregnant patients, but there was no difference in the volume of the stomach contents after 30 min.

These conflicting results may reflect differences in the measurement techniques. It is difficult to quantitate gastric emptying radiologically. Gastric aspiration methods correct for the volume of gastric secretion during the study period, but only allow one single measurement of emptying. Solute absorption has been used widely to measure stomach emptying before surgery, as it is non-invasive and does not require the ingestion of large amounts of fluid [7]. In the present study the rate of paracetamol absorption was used to measure gastric emptying rate during pregnancy and in non-pregnant control subjects.

PATIENTS AND METHODS

Twenty-eight women undergoing termination of pregnancy and 14 non-pregnant women having minor gynaecological surgery were studied. All patients were healthy and none was taking any drugs, including oral contraceptives, which might alter gastric motility. Before surgery the gestation of the pregnant patients was assessed by a consultant gynaecologist, and they were grouped

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TABLE I *Age and weight of patients and duration of fasting (mean (SD))*

Gestation	Age (yr)	Weight (kg)	Starved (h)
Control ($n = 14$)	31.8 (7.5)	59.6 (9.6)	8.0 (4.5)
8–11 weeks ($n = 16$)	25.6 (8.0)	60.3 (11.5)	6.8 (4.1)
12–14 weeks ($n = 12$)	24.8 (8.6)	57.8 (7.3)	5.7 (2.9)

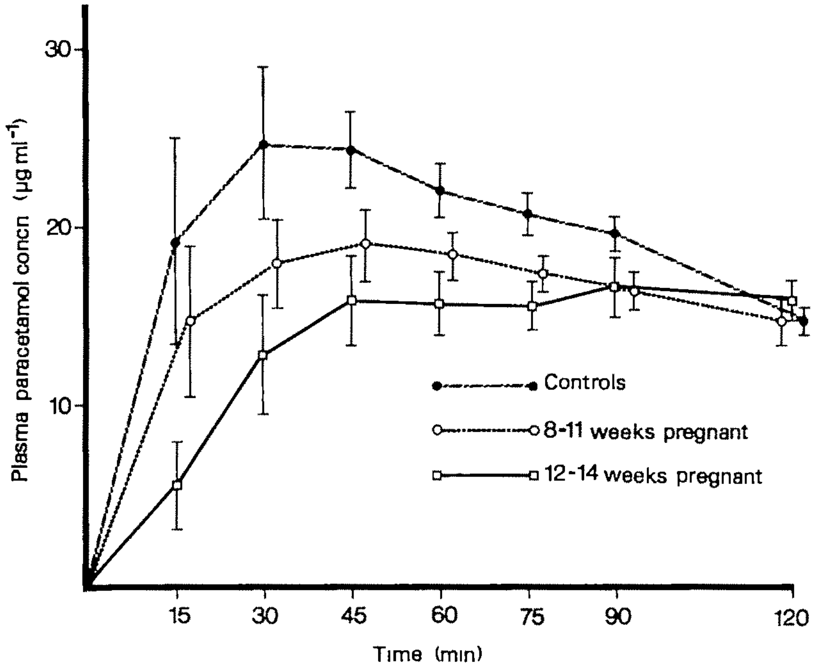

FIG. 1. Mean plasma paracetamol concentrations (±SEM) after paracetamol 1.5 g by mouth with 150 ml of water. Women 12–14 weeks pregnant had significantly lower concentrations at 30, 45 ($P < 0.05$), 60 ($P < 0.01$) and 75 ($P < 0.05$) min compared with controls.

according to the size of the uterus as 8–11 weeks ($n = 16$) or 12–14 weeks ($n = 12$).

Gastric emptying was measured using a paracetamol absorption technique similar to that described by Heading and colleagues [8]. After a fast of at least 4 h each patient took paracetamol tablets 1.5 g (Winthrop Laboratories) with 150 ml of water. Patients remained supine for 2 h whilst blood was sampled at intervals, through an i.v. cannula; blood sampling was completed before the induction of anaesthesia. Plasma samples were frozen at −20 °C and paracetamol concentrations were measured using an enzymatic assay method, specific for the parent compound, which did not detect paracetamol metabolites (Cambridge Life Sciences). The enzyme aryl acylamide amidohydrolase was used to split the amide bond of paracetamol, producing acetate and p-aminophenol. The latter reacted with o-cresol to form a stable blue compound which was measured using a spectrophotometer capable of reading at 615 nm. The procedure was automated to improve the performance of the assay at the low concentrations of paracetamol expected. The system used was a hybrid Technicon AAII/Fisons Vitatron with a Hook and Tucker sampler adapted for the procedure. The external quality control was a commercial kit (American Hospital Supplies), used routinely for measuring therapeutic concentrations of paracetamol in plasma. The coefficients of variation were 0.96% (within batch) and 2.24% (between batch). The assays of 72 patients were reanalysed on a different day and gave a coefficient of varation of 2.35%.

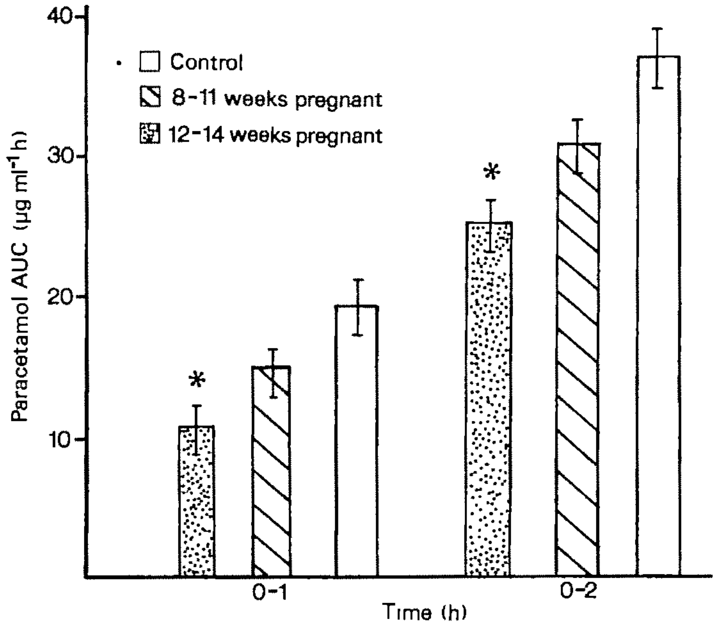

FIG. 2. Mean area under the plasma paracetamol concentration–time curve (AUC) (±SEM) at 1 and 2 h after paracetamol 1.5 g by mouth with 150 ml of water. *Significantly less in women 12–14 weeks pregnant than in controls at both times ($P < 0.05$).

TABLE II. *Peak paracetamol concentrations and time to peak (mean (SEM)) after paracetamol 1.5 g by mouth with 150 ml of water.* *$P < 0.05$ *compared with controls;* †$P < 0.05$ *compared with controls and 8–11 weeks pregnant patients*

Gestation	Peak concn (µg ml^{-1})	Time (min)
Control ($n = 14$)	34.4 (4.3)	45.0 (5.9)
8–11 weeks ($n = 16$)	26.8 (2.7)	46.4 (8.1)
12–14 weeks ($n = 12$)	21.4* (2.2)	71.9† (9.2)

The area under the plasma paracetamol concentration–time curve was calculated using the trapezoidal rule. Data were analysed using one-way analysis of variance for independent samples, followed by Scheffés test where appropriate.

RESULTS

There was no significant difference in age, weight or duration of fasting between the pregnant and control groups (table I).

Plasma paracetamol concentrations were significantly lower at 30, 45 ($P < 0.05$), 60 ($P < 0.01$) and 75 ($P < 0.05$) min in patients who were 12–14 weeks pregnant compared with control subjects. Paracetamol concentrations in the 8–11 weeks pregnant group were between, but were not significantly different from either of, the other two groups (fig. 1). The 12–14 weeks pregnant group had lower peak paracetamol concentrations compared with controls ($P < 0.05$), and showed a delay in the time taken to reach a peak compared with controls and 8–11 weeks pregnant women ($P < 0.05$) (table II).

The areas under the plasma paracetamol concentration–time curve (AUC) at 1 and 2 h were less in 12–14 weeks pregnant patients compared with controls ($P < 0.05$). The AUC in the 8–11 weeks pregnant group were not significantly different from either of the other groups (fig. 2).

DISCUSSION

As paracetamol is not absorbed in the stomach, but is readily absorbed in the upper small bowel, the rate of absorption depends on the rate of gastric emptying. Heading and colleagues [8] demonstrated a significant correlation between the half-time of gastric emptying, measured by sequential gamma scintiscanning of the stomach, and plasma paracetamol concentrations. Therefore, the reduction in mean plasma paracetamol concentrations in the 12–14 weeks pregnant patients, in the present study, represented a delay in gastric emptying. The smaller area under the plasma paracetamol concentration–time curve in these subjects reflected a reduction in paracetamol absorption [9]. Although no statistically significant difference was demonstrated between the control and the 8–11 weeks pregnant patients, the values for the latter group were between the 12–14 weeks and the non-pregnant values.

Inhalation of gastric contents remains an important cause of anaesthetic mortality and morbidity [10]. Many studies have demonstrated large volumes of acid stomach contents in patients prepared for surgery. Hester and Heath [11] reported that, after prolonged fasting, more than 40 ml of fluid was recovered from the stomach of one in eight patients presenting for elective surgery, and over half the patients had gastric contents with a pH of less than 2.5. More than 25 ml of acidic stomach fluid was aspirated from 66% of patients presenting for minor outpatient operations [12]. As many patients undergo surgery during early pregnancy, it may be important to determine whether significant gastric stasis is present at this time. Although the present study demonstrated delayed stomach emptying during pregnancy, it did not show whether this increased the risk of aspiration of gastric contents.

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MALIGNANT HYPERPYREXIA AND SUDDEN INFANT DEATH SYNDROME

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SUMMARY

This paper reports three investigations of the suggested relationship between sudden infant death syndrome (SIDS) and malignant hyperpyrexia (MH). In the first study 151 MH-susceptible families completed a questionnaire designed to identify the incidence of SIDS within their own pedigree. In the second study 106 SIDS families completed a questionnaire designed to identify the incidence of anaesthetic related problems. In the third study, 14 SIDS parents were subjected to muscle biopsy and in vitro *halothane contracture and caffeine contracture screening for susceptibility to MH. From the results of the three studies it can be concluded that there is no association between SIDS and MH.*

In 1982 Denborough, Galloway and Hopkinson [1] stated that three of nine Australian families susceptible to malignant hyperpyrexia (MH) had also suffered the loss of a child through sudden infant death syndrome (SIDS). Until this time there had been no clinical suspicion of an association between these two conditions. This suggested association was avidly promoted by the media and in this country caused concern amongst both the MH and the SIDS families.

A further study [2] described "positive medical family histories" in relation to anaesthesia among SIDS families. We felt it was important to validate this association, studying both the incidence of SIDS in the MH families and the incidence of MH in the SIDS families. A further study was designed in which SIDS parents were asked to submit to a muscle biopsy similar to those performed as part of the routine screening procedure for members of MH families [3].

SUBJECTS, MATERIALS AND METHODS

First study

A simple questionnaire was sent to 195 patients previously biopsied in this department who had been shown to be susceptible to MH (MHS) who were in or above child-bearing age.

The questions included:

How many pregnancies have you had?
What was the outcome of these pregnancies?
How many miscarriages?
How many stillbirths?
How many children died in the first year of life? (Please give dates of birth, death, cause of death as written on the death certificate.)

Second study

Another more elaborate questionnaire was sent to 106 consecutive SIDS parents, through the Foundation for the Study of Infant Deaths. This questionnaire asked for details of the death of the child, including ambient temperatures and clothing, etc., and the anaesthetic histories of both parents and their respective families. SIDS parents were also asked to provide details of any neuromuscular abnormalities including strabismus, ptosis, joint dislocations, hernia, kyphoscoliosis, muscle pains and cramps and the effects of strenuous exercise they experienced.

Third study

Following the publicity in the media, 14 SIDS parents volunteered to undergo a biopsy of the left vastus medialis muscle. These studies were accepted by the Research Ethical Committees of both Leeds East and Leeds West Health Authorities. Halothane and caffeine contracture tests were

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performed *in vitro* using the European MH Group procedure [4, 5] and muscle histology was undertaken. The clinical management of these subjects was identical to that given to patients referred to this Unit for screening for MH susceptibility [3].

RESULTS

First study

One hundred and fifty-one (76%) of the questionnaires were returned, recording 511 pregnancies with 456 live births. The outcome of these live births is summarized in table I.

There were 16 deaths in children younger than 1 year of age, of which three were described as "cot deaths" occurring in apparently healthy infants. The cause of the infant deaths is summarized in table II and details of the SIDS are in table III.

Using the binomial theorem the incidence of SIDS amongst the MH live births does not differ significantly from the incidence of SIDS in the general population ($P < 0.05$), which is taken to be 1.96 per 1000 live births [6] (but see discussion later).

Second study

A total of 278 anaesthetics had been recalled amongst the 106 pairs of SIDS parents who replied to the questionnaire. There were no deaths attributed to anaesthesia and five families recorded a problem which was not suspected to be MH at the time by their medical attendants. Scanty details of these complications were as follows:

TABLE I. *Outcome of pregnancies in MH families*

Total pregnancies	511
Live births	456
Miscarriage	46
Stillbirth	5
Therapeutic termination	3
Ectopic pregnancy	1

TABLE II. *Causes of infant death in MH families*

Perinatal unspecified	6
Congenital heart disease	4
Gastroenteritis	2
Convulsions	1
SIDS	3

TABLE III. *Details of SIDS in MH families*

Case 1. 1962	3 months old	6th pregnancy
Case 2. 1971	5 months old	17th pregnancy
Case 3. 1978	4 months old	4th pregnancy

Subject 1. A father had experienced an increase in postoperative temperature on several occasions.
Subject 2. A mother was pyrexial for 7 days following Caesarean section on two occasions.
Subject 3. A mother reported a postoperative respiratory depression and slow recovery.
Subject 4. A mother described postoperative stiffness for 24 h following the removal of a benign papilloma from the soft palate.
Subject 5. A maternal uncle was "packed in ice" following an acute appendicectomy.

The only case which could have been MH was Subject 5, although it should be noted he was undergoing surgery for an infected lesion, the mobilization of which can cause acute pyrexia. In our experience of over 500 proband investigations for MH screening, postoperative pyrexia has not been found to be a presenting sign of MH. Also, we have never encountered a case of MH presenting as a 7-day postoperative pyrexia. Subject 4 resembles a post suxamethonium myositis. There were no consistent reports of neuromusculoskeletal problems.

Third study

The laboratory tests conducted on live muscle tissue taken from the normal SIDS parents were all within normal limits (MHN) as defined by the European protocol.

In order to compare our studies with those of Denborough, Galloway and Hopkinson [1], muscle specimens were also exposed to 3% halothane, a test not recognized in the European MH Group procedure. One of the 14 parents produced an insignificant increase in the baseline muscle tension of 0.1 g on exposure to 3% halothane.

No patient displayed any abnormal histology, and preoperative resting serum creatinekinase (CK) activity was consistently within normal limits for our laboratory.

DISCUSSION

It was not until 1971 that cot death or sudden death became accepted as a registrable cause of death in England and Wales. The term sudden infant death syndrome (SIDS) came into use in 1979. The incidence of SIDS in the general population is difficult to ascertain precisely and is variously quoted as 0.62 per 1000 live births in 1971 to 2.13 in 1982 and currently is 1.96 (*vide supra*). Before 1971, unexpected deaths were reported as "sudden respiratory deaths" and as acute tracheobronchitis, bronchiolitis or bronchopneumonia, despite lack of conclusive pathological evidence. However, virological evidence has been found by Downham and colleagues [7] in some sudden respiratory deaths and some "cot deaths". Since 1971 the number of sudden deaths attributed to "respiratory causes" has declined from 1.63 in 1971 to 0.46 in 1981 whereas the combined rate of SIDS and respiratory problems has stayed at a steady 2.4 per 1000 live births over the period 1971–81 [8].

The problem is compounded further because of controversy over the exact definition of SIDS, some applying the term regardless of postmortem findings [9], thus making epidemiological studies difficult. Becroft, Beckwith and Ray in 1970 [10] suggested the definition to be: "the sudden death of an infant or young child, which is unexplained by history, and in which a thorough postmortem examination fails to demonstrate an adequate cause of death".

Because of these difficulties, cases described as "cot deaths" occurring in MH families before 1971, were included. This gives an overall incidence in the MH families of three cot deaths per 456 live births as compared with 2.4 per 1000 live births for the combined SIDS and respiratory deaths in the general population. If these two cases are excluded because they could not have been registered as a SIDS or cot death on the death certificate, the incidence becomes 1 SIDS per 456 live births compared with 1.96 per 1000 live births in the general population; the latter incidence excludes the "respiratory causes" group.

The number of cases of SIDS reported in this study is too small for there to be a significant and specific link between MH and SIDS.

The incidence of anaesthetic mortality in the SIDS group was zero and the morbidity of 5 in 278 anaesthetics is gratifyingly low. With the possible but unlikely exception of Subject 5, none could be considered to be MH reactions.

From a recent study in this laboratory, MH is inherited as a Mendelian dominant characteristic [3], although differing patterns of inheritance have been described previously [11]. Should SIDS correlate with MH, the muscle abnormality should also be dominantly inherited and each SIDS parent should have a 0.5 probability for the muscle abnormality. Using sequential analysis it can be inferred that, with the 14 negative findings, the probability of a muscle defect occurring similar to that found in MHS patients is less than 0.05. We considered that further biopsy studies, with their attendant risks, would be unethical.

The apparent discrepancy between our laboratory results and those of Denborough and colleagues [1] can be explained by the method of case selection used by the latter group. In particular they encouraged SIDS families with a family history of an anaesthetic mishap to be investigated preferentially (Denborough, 1987 personal communication), thus biasing their findings in favour of an association between SIDS and MH, which we have been unable to substantiate.

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POST-TETANIC COUNT AND PROFOUND NEUROMUSCULAR BLOCKADE WITH ATRACURIUM INFUSION IN PAEDIATRIC PATIENTS

S. A. RIDLEY AND D. J. HATCH

SUMMARY

In 38 paediatric surgical patients given atracurium by infusion, the degree of neuromuscular blockade was monitored using the post-tetanic twitch response. This was assessed by counting the number of visible responses when single twitch stimulation was applied at 1 Hz for 30 s after a 5-s tetanic stimulation at 50 Hz. A post-tetanic count of less than 10 correlated with a single twitch height of less than 5% of control, and ensured adequate paralysis. Once the count was greater than 15, the blockade could be antagonized readily.

Atracurium degrades rapidly and, because it is difficult to quantify the train-of-four response accurately by visual or manual estimation [1], coughing, hiccup or ventilatory movements may occur on occasions, despite the use of a peripheral nerve stimulator. To avoid this, complete suppression of the train-of-four (TOF) response is sometimes required. Viby-Mogensen, Howardy-Hansen and Chraemmer-Jorgensen [2] pointed out that it is possible to quantify profound non-depolarizing neuromuscular blockade by counting the number of post-tetanic twitches after a 5-s period of supramaximal stimulation at 50 Hz. The purpose of this study was to correlate the degree of neuromuscular blockade using atracurium with the post-tetanic count (PTC).

PATIENTS AND METHODS

The study was approved by the hospital Ethical Committee; parental consent was not obtained because monitoring of neuromuscular function is commonplace in anaesthetic practice.

Thirty-eight paediatric patients undergoing a variety of surgical procedures requiring mechanical ventilation were studied. All patients were fit (ASA grade I or II) apart from their presenting condition, and were not receiving any drugs that might have interfered with neuromuscular function.

Patients younger than 8 months of age and all neurosurgical patients received atropine 0.02 mg kg^{-1} i.m. 45 min before the induction of anaesthesia. Older children who weighed less than 15 kg were premedicated with Pethidine Compound 0.06–0.08 ml kg^{-1} (1 ml contains pethidine 25 mg, promethazine 6.25 mg and chlorpromazine 6.25 mg). Children weighing more than 15 kg received papaveretum 0.4 mg kg^{-1} and hyoscine 0.008 mg kg^{-1} 90 min before induction.

Anaesthesia was induced with 50% cyclopropane in oxygen or thiopentone 5 mg kg^{-1} depending on their preference and weight. The trachea was intubated in all patients—in neonates while they were awake, and in others with the aid of suxamethonium 2 mg kg^{-1}. Anaesthesia was maintained with 0.5–1.5% halothane and 33% oxygen in nitrous oxide delivered by a paediatric T-piece and bag. The electrocardiogram, arterial pressure (Dinamap), and praecordial heart and breath sounds were monitored in all patients.

A constant current peripheral nerve stimulator (Bard Biomedical) provided supramaximal stimuli for all measurements, via surface electrodes placed over either the posterior tibial nerve behind the medial malleolus or the ulnar nerve at the wrist. Output for maximal twitch response (displayed in milliamperes on the nerve stimulator) was recorded.

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Neuromuscular blockade was produced initially with a single dose of atracurium 0.4 mg kg^{-1} and maintained subsequently with an infusion of undiluted atracurium (initially at 8 μg kg^{-1} min^{-1}) delivered by a Grazeby Dynamics 16A syringe pump. Artificial ventilation was provided using a Nuffield 200 ventilator (Penlon) with a paediatric valve [3]; this converts the machine to a pressure generator and enables it to deliver small tidal volumes.

The intensity of neuromuscular blockade was monitored by assessing the visible twitch in response to the following standard sequence of stimulation, which has been modified from that described by Viby-Mogensen, Howardy-Hansen and Chraemmer-Jorgensen [2]:

(a) a train-of-four, repeated every 12 s, if necessary, for reassessment;
(b) a 30-s delay;
(c) tetanic stimulation (50 Hz) for 5 s;
(d) a 3-s delay;
(e) single twitch stimulation at 1 Hz for 30 s.

The number of visible responses was recorded. The degree of neuromuscular block was first assessed 6 min after the single dose and then at 6-min intervals, so avoiding the effect of tetanic stimulation on the subsequent cycle.

The intensity of neuromuscular blockade was varied according to the following regimen:

(a) If the bolus dose failed to obliterate the train-of-four response, incremental doses of atracurium 0.1 mg kg^{-1} were given at 6-min intervals until this was achieved.
(b) If no post-tetanic twitches were visible after 24 min, the infusion of atracurium was discontinued until the PTC had reached 5. The infusion was then restarted at its previous rate.
(c) If the PTC was decreasing, the infusion rate was halved when the count reached 5. Similarly, if the PTC was increasing, the infusion rate was doubled when it reached 15.
(d) If doubling the rate of infusion failed to bring the PTC below 15, "top up" bolus doses of atracurium 0.1 mg kg^{-1} were given as before.

At the end of the operative procedure, the infusion was discontinued and neuromuscular transmission allowed to recover spontaneously. When at least one response was visible on the TOF, the anaesthetic agents were discontinued and any residual neuromuscular blockade was antagonized with neostigmine 0.05 mg kg^{-1} (plus atropine 0.02 mg kg^{-1}). The times taken from the injection of the reversal agents to the return of the fourth response of the TOF and to the patient making an adequate clinical recovery (as assessed by regular ventilation and purposeful movements) were recorded.

Student's *t*, Chi-squared and Wilcoxon Rank

TABLE I. *Demographic details of patients studied. Standard deviation shown in parentheses*

	Infants (wt < 5 kg)	Small children (5–15 kg)	Older children (> 15 kg)
Number studied	8	11	19
Age: Mean	55 (47) days	1.5 (1) yr	8.3 (4) yr
Range	2–120 days	3 month–3 yr	4–16 yr
Weight (kg) (mean)	2.9 (0.8)	10.1 (2.8)	29 (13)
Time of premedication (min before operation)	52 (19)	68 (22)	96 (35)
Duration of anaesthesia (min)			
Mean	95 (58)	76 (34)	93 (40)
Range	16–181	33–165	47–180
Type of surgery			
Ophthalmic	—	1	2
Abdominal	8	4	4
Neurosurgical	—	3	4
Orthopaedic	—	1	1
Urological	—	1	2
Bone marrow harvest	—	1	1
Plastic surgery	—	—	4
Cardiac catheterization	—	—	1

Sum tests were used for statistical analysis and a P value of less than 0.05 was considered significant.

RESULTS

The age, weight, time of premedication, duration and type of surgery in the 38 patients studied are shown in table I.

In three patients, the infusion of atracurium was withheld because of unexpected changes in the surgical procedure.

In the 12 patients whose posterior tibial nerve was used for monitoring, a maximum twitch response was obtained with a mean output of 20(SD ± 7.8) mA from the stimulator while a mean stimulus of 33(SD ± 17) mA was required ($P < 0.05$) in those in whom the ulnar nerve was used.

The patients were divided into three groups according to weight (< 5 kg, 5–15 kg, > 15 kg), but there were no differences between the groups in the mean initial bolus dose of atracurium required to obliterate the train-of-four response. The overall mean initial bolus dose required was 0.56(SD ± 0.14) mg kg^{-1}.

The mean infusion rates used throughout the procedures for the three groups are shown in table II. The older children required a significantly higher rate of infusion when compared with the younger groups, between whom the different rates were not significant. Three of the 19 older children (> 15 kg) required an additional dose of atracurium compared with five out of the 19 smaller children (> 15 kg). The mean additional single dose was 0.22(SD ± 0.1) mg kg^{-1}, administered an average of 50(SD ± 6) min after the initial bolus, and did not vary between the three groups. The duration of anaesthesia in those patients who required an additional dose was 116(SD ± 15) min and this was significantly longer ($P < 0.05$) than in patients who did not require an extra dose (mean duration of anaesthesia 80(SD ± 7) min.

TABLE II. *Mean (SD) infusion rates in three patient groups. *P < 0.05 compared with younger groups*

Infants (< 5 kg)	Small children (5–15 kg)	Older children (> 15 kg)
7.9 (0.63)	7.4 (0.74)	8.6* (1.25)

The increase in PTC with time as neuromuscular function recovered spontaneously with and without the effect of the infusion is shown in figure 1. Recovery was similar up to 36 min, after which time the infusion significantly slowed the return of function.

Figure 2 illustrates the relationships between the increasing PTC and the return of the response to train-of-four stimulation. The return of the full

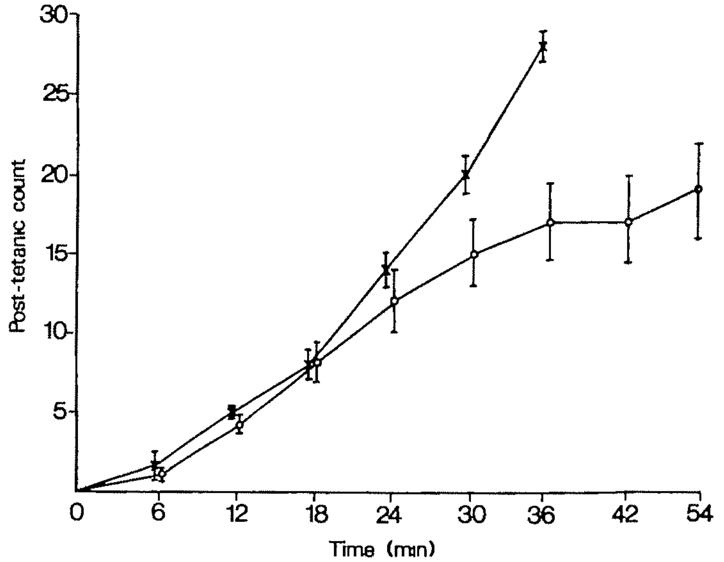

FIG. 1. The PTC (mean ± SEM) increasing as neuomuscular function recovers spontaneouly (X) and under the effect of the infusion (O).

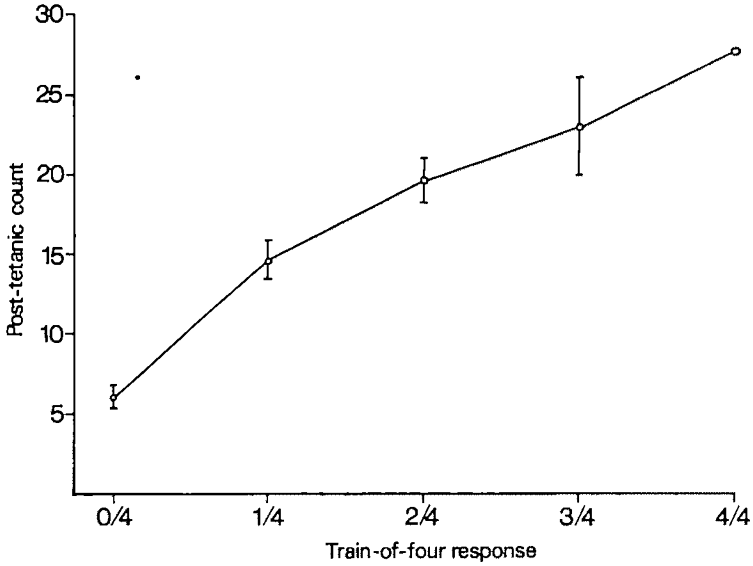

FIG. 2. The relationship between the PTC (mean ± 95 % confidence limits) and the train-of-four response.

TOF and clinical recovery took longer than 5 min from injection of the reversal agents in one patient. This patient received a total initial dose of 0.8 mg kg^{-1}, since some of the atracurium was suspected of being administered extravascularly by accident. Reversal was attempted only 18 min after this dose. The patient made a full recovery 8 min after the administration of the anticholinesterase.

DISCUSSION

The mean initial dose of atracurium 0.56 mg kg^{-1} for infants and children was higher than might be expected; however, it agrees with the findings of Nightingale and Bush [4] whose paediatric patients required 0.6 mg kg^{-1} for intubation when assessed on clinical grounds. When more sensitive monitors of neuromuscular function such as twitch tension and electromyography were used, smaller bolus doses were reported (for example 0.3 mg kg^{-1} [5] and 0.4 mg kg^{-1} [6]). The incremental method used in this study, in which each additional dose of atracurium was given at 6-min intervals, will tend to increase the dose required for a given effect.

Goudsouzian and colleagues [7] reported a mean infusion rate of atracurium during halothane, oxygen and nitrous oxide anaesthesia as 8.3 μg kg^{-1} min^{-1}—a value which agrees closely with our findings. The concentration of atracurium at steady state is given as:

$$C^{ss} = \text{infusion rate} \times \text{clearance}$$

As no statistical differences in atracurium clearance have been reported between small and older children [8], the lower rate of infusion in children weighing less than 15 kg in the present study would imply that a lower concentration of atracurium was required to achieve the same degree of neuromuscular blockade, and may reflect increased sensitivity, as shown by Goudsouzian, and colleagues [9].

The number of patients who required an additional single dose at some time during anaesthesia was the same in infants and young children weighting less than 15 kg and those children weighing more. This would suggest that the intensity of neuromuscular blockade was similar in both groups and that the different infusion rates reflected a genuine difference in sensitivity.

The patients who required an additional dose did have a significantly longer anaesthetic and this suggests that the infusion rates in this study were not the most suitable for procedures lasting more than 80 min. This is also reflected in the fact that the recovery of the PTC was only marginally slowed by the infusion in the first 30 min, at which time the PTC had reached 15. Although recovery of blockade after this was delayed more markedly by the infusion, at 30 min the level of neuromuscular function was 10–20 %.

The larger supramaximal stimulus required when stimulating the ulnar nerve compared with the posterior tibial nerve may be a reflection of the deeper position of the ulnar nerve at the wrist compared with that of the posterior tibial at the ankle.

The spontaneous degradation of atracurium occurs rapidly and, once recovery of neuromuscular function has begun, it continues to improve rapidly. Goudsouzian and co-workers [9], studying infants anaesthetized with halothane, oxygen and nitrous oxide, and given a bolus of atracurium 0.4 mg kg^{-1}, showed that once recovery had started the single twitch response moved from 5 % to 25 % of its control value in a mean of 8.5 min. Unless the single twitch is kept at less than 10 % of its control value or the train-of-four response kept to 25 % [10] ventilatory movements, cough and hiccup may occur [11].

In the present study the spontaneous recovery of neuromuscular function took longer than was found by Goudsouzian and colleagues [9]. The time taken to recover from 5 % twitch height (equivalent to one response on the TOF) to 25 % twitch height (three out of four in the TOF) was approximately 12 min. The use of the infusion plus the bolus dose may explain the longer recovery time obtained in the present study.

Heisterkamp, Stansted and Cohen [12] described enhancement of the post-tetanic twitch tension (post-tetanic facilitation) in partially curarized patients. Viby-Mogensen, Howardy-Hansen and Chraemmer-Jorgensen [2] demonstrated that this still occurred with profound neuromuscular blockade and that the response to post-tetanic twitch stimulation after injection of non-depolarizing neuromuscular blockers appeared earlier than the pre-tetanic twitch or train-of-four response. These investigators showed that the time of return of train-of-four responses could be derived from the number of post-tetanic twitch responses when pancuronium was used.

Figure 2 shows that when the PTC was less than 10, all the responses of the train-of-four were obliterated. If the PTC was kept in single figures, the height of the single twitch was less than 5 % of its control value and cough, hiccup and ventilatory movements could be avoided. This is particularly important in neurosurgery and ophthalmic surgery, where the duration of surgery is hard to predict and movements of the patient could be disadvantageous. A decreasing PTC indicates an increasing intensity of neuromuscular blockade and so allows appropriate action to be taken. Similarly, towards the end of surgery, the intensity of blockade may be adjusted by simply counting the PTC rather than endeavouring to estimate the train-of-four ratio which is difficult without complex monitoring equipment. This allows easy antagonism of the neuromuscular blockade.

Our results suggest that following an initial bolus of 0.5 mg kg^{-1}, an infusion rate of 8 μg kg^{-1} min^{-1} will lead to a gradual decrease in the intensity of neuromuscular blockade, especially in children weighing more than 15 kg. Using this basic infusion rate as a guideline, and adjusting it to keep the PTC between 5 and 10, will ensure adequate paralysis throughout the period of surgery. Complete antagonism of neuromuscular blockade can be expected within 6 min of injection of the anticholinesterase.

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COMPARISON OF RECOVERY AFTER NEUROMUSCULAR BLOCKADE BY ATRACURIUM OR PANCURONIUM

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SUMMARY

Thirty patients were randomly allocated to receive either atracurium or pancuronium for neuromuscular blockade during surgery. At the end of the operation residual paralysis was antagonized with neostigmine. Voluntary strength was assessed at intervals after the antagonism, by observing grip strength, maximum inspiratory and expiratory force, 5-s head lift and the presence or absence of double vision. Grip strength and maximum expiratory force recovered significantly more quickly in the atracurium group over the 2-h measurement period. Double vision was significantly more frequent at up to 1 h when pancuronium had been used. At no time was there any significant difference between the two groups in respect of the 5-s head lift or, after 30 min, in the measurement of inspiratory force.

During routine anaesthesia a clinical impression was gained that the recovery of peripheral muscle power was quicker and more complete if atracurium rather than pancuronium had been used as the neuromuscular blocking agent. To our knowledge there is no published work which compares the rates of recovery of voluntary muscle power following muscle paralysis with either of these two drugs. The present study was undertaken to test the validity of this clinical observation. A preliminary report of this work has been presented to the Anaesthetic Research Society [1].

PATIENTS AND METHODS

The local ethics committee approved of the project and informed verbal consent was obtained from the patients.

Thirty patients (ASA Class I–II) undergoing minor surgery which did not affect the diaphragm, abdominal muscles or the dominant hand were randomly divided into two equal groups. All received temazepam 10 mg by mouth 1 h before the induction of anaesthesia with fentanyl 2 $\mu g\ kg^{-1}$ i.v. and sufficient thiopentone to obtund the eyelash reflex. Immediately following the onset of sleep (during which time there was spontaneous or assisted ventilation through an anaesthetic facemask with 77% nitrous oxide in oxygen), surface electrodes were placed over the ulnar nerve of the non-dominant hand at the wrist. Immediately following the induction of anaesthesia these were connected to a peripheral nerve stimulator (Bard Biomedical Model 750 Digital) which was adjusted to produce a supra-maximal stimulus. One group (six females, nine males; mean age 41.2 yr, range 18–58 yr; mean weight 68.7 kg, range 45–95 kg) then received pancuronium 0.08 $mg\ kg^{-1}$ i.v. and the other (seven females, eight males; mean age 30 yr, range 18–57 yr; mean weight 66.5 kg, range 49–81 kg) received atracurium 0.3 $mg\ kg^{-1}$ i.v. After intubation of the trachea, maintenance of anaesthesia was by ventilation to normocapnia with 77% nitrous oxide in oxygen. Normocapnia was achieved by using a fresh gas flow of 70 $ml\ kg^{-1}$ via a Bain breathing system [2].

Neuromuscular blockade was monitored throughout anaesthesia by the response to the train-of-four stimulation [3] administered at intervals of not less than 12 s. Supplementary

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doses, equal to one-quarter of the initial dose of atracurium or pancuronium, were given during surgery whenever the third component of the train-of-four became palpable to the observer.

Increments of fentanyl 1 μg kg^{-1} were given if the patient's arterial pressure exceeded the pre-induction value by more than 20 mm Hg or if the heart rate exceeded 85 beat min^{-1}.

When surgery was completed, anaesthesia was continued in both groups until the third component of the train-of-four was just palpable. Residual neuromuscular block was then antagonized with neostigmine 2.5 mg and atropine 1.2 mg. Nitrous oxide was discontinued and the lungs ventilated with 100 % oxygen from the time of the administration of neostigmine.

Postoperative analgesia was accomplished with local anaesthetic blockade or paracetamol. The need to use opioids for pain relief excluded the patient from the study.

Before premedication and at 30, 60, 90 and 120 min after neostigmine each patient completed five tests of muscle power in the order described below. The same person supervised the pre- and postoperative tests, but was not aware of which neuromuscular blocking agent had been used. The tests were as follows:

(i) *Grip strength* was measured as the ability of the dominant hand to compress a fixed volume of gas in a 50-ml syringe. The patient's grip on the syringe was standardized with the ball of the thumb on the plunger and the terminal interphalangeal joints of the index and middle fingers supporting the lugs on the barrel. The volume of gas chosen (typically 20 ml for the average hand) was that which allowed the patients to adopt the standardized grip comfortably. The force the patient was able to develop was measured as the pressure on a Bourdon pressure gauge (fig. 1). An average value for five attempts in 15 s was recorded on each occasion.

(ii) The *maximum inspiratory force* was measured by requesting the patient to inhale as hard as possible from residual volume via a well fitting mouthpiece connected to a Bourdon pressure gauge (fig. 1). The nose was occluded with a clip. An average of three attempts was recorded.

(iii) Using a technique similar to (ii) above, the *maximum expiratory force* was measured by allowing the patient to exhale from maximum lung volume.

(iv) The presence of *diplopia* was assessed by holding up a white card with a single black line on

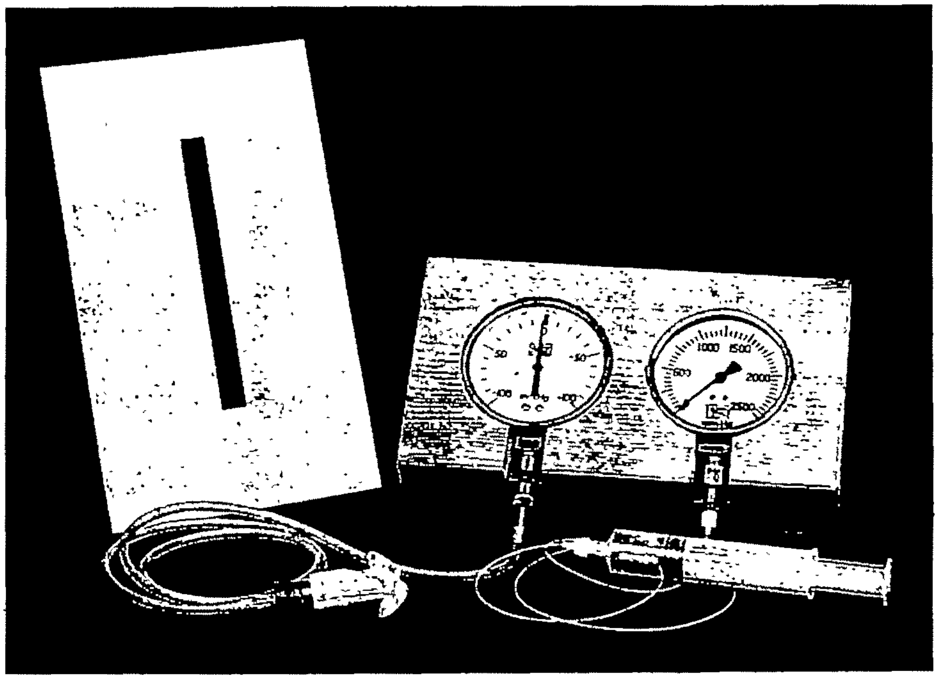

FIG. 1. Equipment used for quantitative assessment of grip strength, inspiratory and expiratory forces and double vision.

TABLE I. *Numerical data on magnitude and timing of drug dosages. There are no significant differences between the two groups with respect to the dose of thiopentone used, the number of patients receiving supplementary doses of fentanyl and the method of obtaining postoperative analgesia. As expected from the design of the study and as explained in the text, the number of patients requiring supplementary doses of neuromuscular blocker and the time between the onset of relaxation and antagonsim differed between the two groups*

	Atracurium group	Pancuronium group
Dose of thiopentone (mg) (mean ± SD)	281 ± 56	315 ± 55
Number of patients receiving supplementary doses of neuromuscular blocker	13	8
Number of patients receiving supplementary doses of fentanyl	6	7
Number of patients given local anaesthesia for postoperative analgesia	10	9
Time from administering the first dose of blocker to administering neostigmine (min)	38.1 ± 15.9	53.1 ± 20.3

it (fig. 1) at the periphery of the patient's visual field.

(v) The ability to *lift the head* clear of the pillow for 5 s was recorded as yes or no.

RESULTS

Data on the induction dose of thiopentone, the number of supplementary doses of neuromuscular blocking drug and fentanyl, the method of postoperative analgesia and the duration of anaesthesia are given in table I.

The results of tests (i), (ii) and (iii) are shown graphically in figures 2, 3 and 4, respectively, and the results of tests (iv) and (v) are shown as tables II and III, respectively. In the statistical analysis subsequently described, values of $P > 0.05$ were regarded as being not significant (ns).

In figures 2, 3 and 4 the results at the various time intervals are not superimposed, only for the sake of clarity: they were all taken at the predetermined times. In analysing the results for grip strength, inspiratory and expiratory force, the variable of interest is how quickly the patients regained their preoperative muscle power. Although the statistical results were calculated on raw data, the performance of each patient in each test has been expressed as a percentage of that patient's control response. The results at 30, 60, 90 and 120 min have been plotted for each group.

As the patients gradually recovered to their normal state, the statistical distribution of deviations from control values became progressively skewed with time as more and more of the patients had a zero or near zero deficit in recorded power. Because of this the means and standard deviations of the populations are not recorded. Instead, the range and median values have been plotted. Since there were 15 patients in each group, there were results from seven patients between the median and the upper range bar and seven results between the median and lower range bar in figures 2,3 and 4. Where a range bar is not shown, all the recordings are contained within the size of the median circle.

In the analysis of the results the question asked was "Is there a statistically significant difference between the strength of the atracurium and pancuronium groups at 30, 60, 90 and 120 min as compared with their control values?" To assess

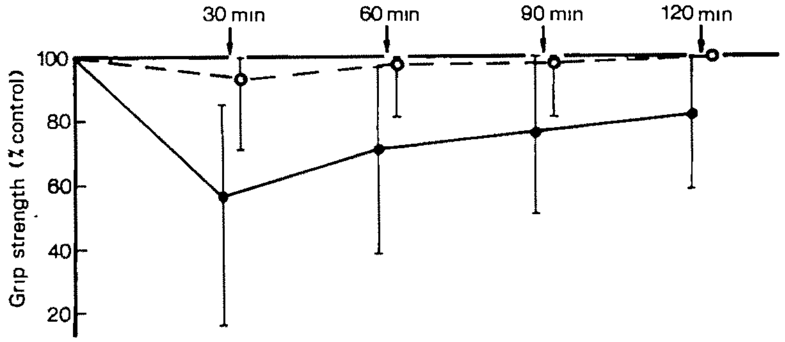

FIG. 2. Recovery of grip strength (median ± range) after antagonism of atracurium (○) or pancuronium (●). The difference between the groups was significant ($P < 0.001$) at each time.

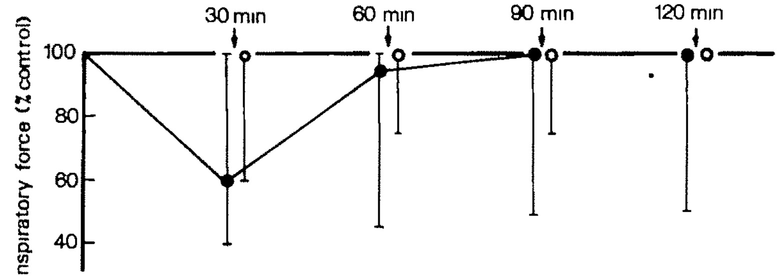

FIG. 3. Recovery of inspiratory force (median ± range) after antagonism of atracurium (○) or pancuronium (●). Differences between groups significant ($P < 0.05$) only at 30 min.

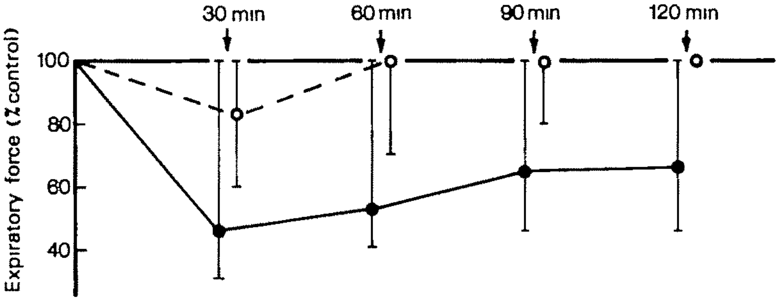

FIG. 4. Recovery of expiratory force (median ± range) after antagonism of atracurium (○) or pancuronium (●). Differences between groups significant ($P < 0.001$) at each time.

this, the deficits in muscle power between the individuals in the atracurium and pancuronium groups when related to their own control values were compared using a Wilcoxon rank sum test [4]. The P values testing the null hypothesis that there was no significant difference between the two groups are given in the legends to figures 2,3 and 4.

TABLE II. *Number of patients in each group suffering from double vision*

	30 min	60 min	90 min	120 min
Atracurium ($n = 15$)	1	0	0	0
Pancuronium ($n = 15$)	8	5	1	0
P	< 0.01	< 0.05	ns	ns

TABLE III. *Number of patients in each group who could not head lift for 5 s*

	30 min	60 min	90 min	120 min
Atracurium ($n = 15$)	0	0	0	0
Pancuronium ($n = 15$)	2	0	0	0
P	ns	ns	ns	ns

In tables II and III the null hypothesis that there was no significant difference in the distribution of the presence of double vision and the ability to lift the head for 5 s between the two groups when compared with the control values was tested using Fisher's Exact Probability test. The results are shown as P values below the tables.

DISCUSSION

It has been known for many years that there is considerable variation in the relative sensitivity of different muscle groups to a given dose of neuromuscular blocking drug. Studies have consistently indicated that the muscles of ventilation preserve adequate function long after the grip strength, head lifting ability and the ophthalmic muscles have been severely affected [5,6]. There have also been several papers which have attempted to correlate evoked responses from single twitch, tetanic and train-of-four stimulation with clinical measurements of voluntary muscle power [7–9]. More recently [10], an armlift test has been found to be a more discerning measure of recovery from neuromuscular blockade than a headlift test.

This study has attempted to compare recovery of voluntary muscle power following atracurium or pancuronium. The initial doses of atracurium and pancuronium were chosen in an attempt to produce the minimum dose of each which would reliably allow intubation. The dose of pancuronium which produces 95% twitch depression varies between different studies. Values of 62.2 μg kg^{-1}, 64 μg kg^{-1} and 70 μg kg^{-1} have been quoted by different authors [11–13]. The dose of atracurium which causes 95% twitch depression has been found to be between approximately 200 μg kg^{-1} and 305 μg kg^{-1} and to depend on the method used to determine the dose-response relationship [12, 14–16]. Gramstaad and Lilleaassen [12] determined dose–response curves for atracurium and pancuronium using the same methods. They quoted values for 95% twitch depression of 279.3 μg kg^{-1} for atracurium and 64.4 μg kg^{-1} for pancuronium.

It is possible, therefore, that the patients in our study who received pancuronium 0.08 mg kg^{-1} initially had a marginally greater degree of neuromuscular block than those receiving atracurium at 0.3 mg kg^{-1}. In addition, it can be seen from table I that more patients in the atracurium group required additional doses of neuromuscular blocker than in the pancuronium group, and in view of the known properties of these two drugs this would be expected. It should, however, be remembered that this study measured the *recovery* following antagonism of a given degree of neuromuscular blockade and that considerations relating to the onset or maximal blockade induced by these agents were of subsidiary importance.

Equipment for the quantitative assessment of neuromuscular blockade was not constantly available during this project. Anticipating this, we undertook a preliminary study using a force displacement transducer to measure the force of thumb adduction in order to identity an end-point capable of being detected reliably by palpation alone which correlated well with results from quantitative measurement. This was found to be when the third twitch in response to train-of-four stimulation was just discernible by palpation. It was decided to use this point as that at which the anticholinesterase drug would be administered in the study.

The concept of equivalent degrees of residual blockade is itself not without problems, since different drugs induce different amounts of tetanic or train-of-four fade for any given degree of neuromuscular blockade [17, 18]. Furthermore, the amount of fade at any chosen degree of neuromuscular blockade following atracurium has been shown to be dose-dependent [19]. Our choice of the third component of the train-of-four is, however, easily reproducible and as logical as any other selected end-point.

It can be seen from table I that the time between giving the neuromuscular blocker and antagonizing its action was greater in the pancuronium group. This was not because the patients were undergoing more lengthy surgical procedures, but because anaesthesia in the pancuronium group had to be extended more frequently than in the atracurium group to enable the reversal criterion based on the train-of-four response to be met.

Although neostigmine 2.5 mg is probably adequate to antagonize neuromuscular blockade induced by atracurium when some spontaneous recovery from blockade has already occurred [20], some may question the adequacy of this dose for the antagonism of neuromuscular blockade induced by pancuronium. Viby-Mogensen, Jorgensen and Ording [21], in an uncontrolled study, suggested that neostigmine 2.5 mg may be insufficient for the adequate antagonism of a non-depolarizing block induced by pancuronium, gallamine or tubocurarine, but no measurements were made, before antagonism, of the degree of that block. However, when pancuronium was studied by Katz [22], he found that when the twitch height was greater than 20% of the control height, neostigmine 2.5 mg was adequate for complete antagonism. In addition, Miller, Larson and Way [23] found that, in patients paralysed with pancuronium and in whom blockade was antagonized at 5% recovery of twitch height, none needed more than 2.5 mg to achieve full recovery of the control twitch height. In the preliminary studies described above it was found that, when the third component of the train-of-four was just palpable, the height of the first twitch was always greater than 20% of that of the control twitch height. Consequently it was decided that neostigmine 2.5 mg was, under the conditions of our study, adequate for antagonism in both the atracurium and the pancuronium groups.

Figure 2 shows that the grip strength of the patients in the pancuronium group was significantly weaker for up to 120 min when compared with that of the atracurium group. The patients were asked to perform five compressions of gas in 15 s because, initially, it was thought that they might show different rates of tiring and that this could become another variable of interest. However, in practice this did not occur and what variability there was in the maximum pressure recorded with each compression was the result of minor changes in patient effort and in the position of the thumb and the first and middle fingers on the syringe. Therefore, the average of five attempts was taken. It is pertinent to remember that, if "tiring" had occurred, it would not have been exactly equivalent to fade as seen during tetanic stimulation of a peripheral nerve, because each compression of the syringe is itself the result of a tetanic muscular contraction. The grip test was an easy postoperative test for the patients to perform and provided good separation between the pancuronium and atracurium groups.

Before recording the results of tests of inspiratory and expiratory force (figs, 3, 4) the patients were shown how to use the mouthpiece and nose clip properly. They were taught how to perform the measurements with the glottis open and to avoid trick manoeuvres such as artificial coughing and sucking in with the cheeks. Failure to do this properly led to the patient being excluded from the study. It can be seen from figure 3 that, at 60 min and later, there was no difference between the groups in respect of inspiratory muscle power, whereas figure 4 demonstrates continued failure of recovery of expiratory force for up to 120 min in the pancuronium group. Figure 4 (expiratory force) is in fact very similar to figure 2 (grip strength) in its behaviour and perhaps this is to be expected, since both these tests are measuring the recovery of striated muscle. Taking figures 2, 3 and 4 together demonstrates the truth of the long held belief of anaesthetists that the diaphragm recovers before peripheral muscle following neuromuscular blockade—as has been confirmed recently by Astley and colleagues [24].

Residual neuromuscular block is, in a sense, similar to a myopathy or myasthenic state, both of which frequently produce diplopia. Normal binocular vision is an active process depending largely upon the degree of tone in the medial rectus muscles and occular divergence is therefore to be expected after the administration of a non-depolarizing neuromuscular blocking agent [25]. The extent of this divergence can be used as a sensitive measure of neuromuscular recovery and has been quantified by the use of the Maddox Wing [26]. When there is any weakness of the external occular muscles, the separation of the images increases the further the eyes are voluntarily moved in the normal direction of pull of the paralysed muscle [27]. Consequently, as a simple test for incomplete recovery of the extra-ocular muscles, the white card with the black bar (fig. 1) was held up at the periphery of the patient's visual field to test for double vision. Table I shows that the pancuronium group had significantly more double vision for up to 60 min.

Table II demonstrates that the 5-s head lift is a very insensitive test of complete antagonism of neuromuscular blockade since there was never any difference between the atracurium and pancuronium groups.

Our results show that the standard clinical tests of adequate neuromuscular function, namely the 5-s head lift and the ability to "take a deep breath", although probably adequate for patients to be returned safely to the ward, do not mean that the patient can develop full power in peripheral voluntary muscles.

Atracurium is rapidly broken down by ester hydrolysis and Hofmann elimination [28]. Previous studies on unconscious patients have demonstrated that the rate of recovery is more rapid using atracurium rather than pancuronium [29]. However, to our knowledge, there have been no comparative studies of the return of voluntary muscle power. It is clear from our results that atracurium is the superior agent. The improved grip strength and absence of double vision suggest that it may be a better agent than pancuronium in situations where the rapid return of full muscle power is required. Thus it may be preferred for outpatient anaesthesia, in the elderly and debilitated, and in patients with chronic obstructive airways disease who need expiratory power for effective coughing. In addition, patients given atracurium appeared to be more alert in the initial postoperative period than those given pancuronium. No formal testing of this was carried out.

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OUTCOME AFTER GENERAL ANAESTHESIA FOR REPAIR OF FRACTURED NECK OF FEMUR

A Randomized Trial of Spontaneous v. *Controlled Ventilation*

S. A. COLEMAN, W. J. BOYCE, P. H. COSH AND P. J. McKENZIE

SUMMARY

One hundred and fifty-two patients undergoing surgery for fractured neck of femur were randomly allocated to receive either general anaesthesia with spontaneous ventilation with nitrous oxide and halothane in oxygen or general anaesthesia with controlled ventilation with fentanyl, nitrous oxide and halothane in oxygen. Atracurium was used to provide muscle paralysis in 65% of the latter group, the remainder receiving no neuromuscular blocking agent other than suxamethonium for intubation. Patients were followed up for 6 months. Mortality and outcome were not significantly different between the groups. Overall mortality at 4 weeks was 5.2%, and at 6 months was 15.1%—figures which are considerably lower than in some other comparable studies. This study does not support the suggestion that general anaesthesia with controlled ventilation is associated with increased postoperative mortality.

There is clear evidence in the literature that anaesthetic technique affects outcome after surgery for fractured neck of femur. Subarachnoid anaesthesia is associated with a reduced mortality in the first 2–4 weeks after surgery [1, 2]; however, 2 months after the operation this early advantage had disappeared. After 1 year, mortality was independent of anaesthetic technique [2, 3].

The use of ketamine as sole anaesthetic agent has been shown to be associated with a decrease in the early postoperative mortality in comparison with a control group receiving conventional "relaxant" anaesthesia [4]. However, the reduction in mortality was again of short duration, and no advantage could be demonstrated with long-term follow up.

In the studies of McLaren, Stockwell and Reid [1] and Spreadbury [4], mortality in the groups who received a technique of general anaesthesia which included controlled ventilation and neuromuscular blockade was very high in the first 4 weeks after surgery, being more than 30% in both studies. Spreadbury [4] stated that "the mortality after 'relaxant' anaesthesia for these operations is unacceptable."

The present study was intended to clarify this issue by comparing outcome up to 6 months after operation for fractured neck of femur in patients allocated randomly to receive general anaesthesia with either spontaneous or controlled ventilation. A non-depolarizing neuromuscular blocking drug (atracurium) was used, in small dosage, only if considered necessary on clinical grounds.

The study was approved by the local Ethics committee who did not consider informed consent to be appropriate, and thus it was not sought.

PATIENTS AND METHODS

One hundred and sixty patients undergoing operative repair of intertrochanteric or transcervical fracture of the femur in the John Radcliffe Hospital, Oxford were allocated randomly (on the opening of an envelope just before the induction of anaesthesia) to receive general anaesthesia either breathing spontaneously (group 1) or with controlled ventilation (group 2).

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TABLE I. *Patients excluded from trial before operation or during the operation (conversion to IPPV) (one for each reason)*

Excluded before operation
Inadequate preoperative hydration
Recent head injury
History of episodic hypotension
Electrocardiac evidence of multifocal ventricular ectopic beats
Chronic obstructive airways disease with preoperative hypoxaemia
Excluded during operation
Hypoventilation and multiple ventricular ectopic beats during spontaneous ventilation
Inadequate tidal volume; excessive ventilatory effort
Excessive ventilatory effort with non-inflation of left lung (after conversion to IPPV, found to have profuse purulent secretions blocking airways)

Patients were not considered for inclusion if they were younger than 35 years of age or if the fracture was pathological. A further eight patients were excluded for the reasons shown in table I. All patients received i.v. fluid in the preoperative period. None received formal premedication, but analgesia was given if required.

Anaesthesia was induced in all patients with etomidate 0.2–0.3 mg/kg body weight i.v. Suxamethonium 50–100 mg i.v. was given to facilitate tracheal intubation. Group 1 patients were allowed to breathe spontaneously via a Mapleson A breathing system. Lung ventilation in group 2 subjects was controlled using a Penlon Nuffield 200 ventilator attached to a Bain anaesthetic system supplied with a fresh gas flow of 100 ml/kg body weight. The anaesthetic gas mixture used throughout the study was 66% nitrous oxide and 0–1.5% halothane in oxygen. Balanced anaesthesia in group 2 was supplemented with small increments of fentanyl 25–100 µg given i.v. when indicated clinically. If, in addition, neuromuscular blockade was needed to allow adequate control of lung ventilation, atracurium 0.3 mg/kg body weight i.v. was administered. Residual neuromuscular blockade was antagonized at the end of operation when deemed necessary on the basis of the total drug dose given and the time elapsed since the last increment of atracurium.

A non-depolarizing myoneural blocking drug was given to 50 (64.9%) of the patients in group 2 and antagonism of neuromuscular blockade with neostigmine (and atropine) was required in nine (18%).

Supplementary oxygen was administered continuously to both groups, for 6 h from the moment of discontinuation of the anaesthetic gases, via a Hudson's type facemask at a flow rate of 4 litre min^{-1}.

In one patient halothane was contraindicated and enflurane was substituted.

All anaesthetics were administered by members of the Nuffield Department of Anaesthetics, Oxford, and anaesthetists were asked to record an assessment of the cardiovascular, ventilatory, neurological and general fitness of the patient before operation using the following scoring system:

1 = Normal or minor defects;
2 = significant disorders of moderate severity;
3 = Severe or multiple disorders.

In the "general" assessment, 1 was equivalent to ASA I–II, 2 to ASA III, and 3 to ASA IV or V.

In addition, age, time lapse from admission to operation, past medical history, medication, operative procedure, anaesthetic drugs and doses, preoperative and intraoperative fluid balance, and presence or absence of untoward events during anaesthesia were recorded.

Six months after operation all surviving patients were visited and completed an interviewer-administered questionnaire, giving details of their progress since leaving hospital. Similar information was obtained from the General Practioners for those patients who had died.

Characteristics and outcomes in the two groups were assessed using contingency testing (either χ^2 or Fisher's Exact Probability test, as appropriate). The mortality in the two groups was compared using the Standard Error of the Difference between Proportions. Levels of probability of 0.05 or less were considered to be statistically significant.

RESULTS

The distributions of age, sex, pre-operative condition and interval between admission to hospital and operation are displayed in table II. The average age of the patients in this study was 79 years; 78% were female. The average time between admission and operation was 1.5 days. None of these values differed significantly between the two groups. There was no significant difference in the distribution of the preoperative conditions of patients in the two groups.

TABLE II. *Details of patients studied*

	Group 1 (SV) ($n = 75$)	Group 2 (IPPV) ($n = 77$)
Age (yr) (mean ± SEM)	80.5 ± 1.35	77.7 ± 1.16
Sex (M/F)	12/63	22/55
Fitness		
Grade 1	32	28
Grade 2	38	41
Grade 3	5	8
Mean time admission to operation (days)	1.5 ± 0.17	1.4 ± 0.13

Table III lists the outcome or location of patients at 6 months. One hundred and twenty-two patients were originally admitted from their own homes. Six months later, 88 of these had returned home, 20 had been rehoused, usually in some form of institution, and 14 had died.

The probabilities of these three outcomes were similar in the two groups (χ^2 (2df) = 2.18 (ns)). Of the 30 patients originally admitted from an institution, 21 had returned there and nine had died. Although seven of these deaths occurred in group two, the difference was not quite significant (Fisher's exact probability (2df) = 0.064).

The number of deaths that occurred in each group at 2, 4 and 12 weeks after operation are shown in table IV and are identical. Twenty-six weeks after surgery there had been nine deaths in group 1 and 14 deaths in group 2. This difference was not statistically significant, being only 1.06 standard error.

The mean length of stay (± SEM) in the acute hospital was 20.4 days (±3.3) for group 1 and 19 days (±1.4) for group 2. In summary, there were no statistically significant differences in short- or long-term outcome between the groups, although there was a proponderence of deaths occurring in the IPPV group amongst patients admitted from institutions.

DISCUSSION

With the techniques applied in this study there were no detectable differences in outcome between the two anaesthetic groups. In addition, it is notable that the mortality figures were lower than in some other comparable studies in which anaesthetic technique has been stipulated; in particular, the overall mortality in the first 4 weeks after surgery was 5.2%, in comparison with figures of 31% [1], 32% [4] and 18% [2]. The last of these studies used spontaneous ventilation, whereas the other two studies used controlled ventilation with use of non-depolarizing myoneural blocking drugs.

The result of the present study indicates that a technique utilizing controlled ventilation is safe for patients with fractured neck of femur either

TABLE III. *Outcome or location of patients at 6 months*

	Group 1 (SV)	Group 2 (IPPV)	χ^2
Admitted from home			
Died	7	7	ns
Returned home	39	49	ns
Relocated	13	7	ns
Admitted from institution			
Died	2	7	ns
Returned to institution	14	7	ns

TABLE IV. *Cumulative mortality*

	Time after operation (weeks)			
	0–2	0–4	0–12	0–26
Group 1 SV ($n = 75$)	3 (4%)	4 (5.3%)	9 (12%)	9 (12%)
Group 2 IPPV ($n = 77$)	3 (3.9%)	4 (5.2%)	9 (11.7%)	14 (18.2%)

when non-depolarizing neuromuscular blockers are avoided or when atracurium is used in low dosage. Atracurium was chosen as being unlikely to produce residual paralysis in the postoperative period in the elderly [5].

Valentin and colleagues [3] compared spinal and general anaesthesia in relation to the surgical repair of fractured neck of femur and also found mortality results similar to those of the present study in their spinal anaesthesia group, and slightly higher early mortality at 4 weeks, of 7.5%, in their general anaesthetic group (controlled ventilation with neurolept or enflurane supplementation). Late mortality was very similar to that in the present study in both groups.

There are several possible explanations for the relatively low mortality observed in the present study. In particular, Oxfordshire's elderly population has better than average health and socio-economic status (the Standardized Mortality Rate for all causes is about 90% of the National average).

McLaren, Stockwell and Reid [1] used pancuronium 0.1 mg kg^{-1} to achieve muscle paralysis and patients in the study of Spreadbury [4] received (with one exception) "standard doses" of tubocurarine, alcuronium or pancuronium.

It is possible, as suggested by McLaren, Stockwell and Reid [1] that, in patients receiving the "long-acting" neuromuscular blockers, there may have been some residual effect in the postoperative period, which might have increased the likelihood of stasis and subsequent deep venous thrombosis. The ability to cough may also have been impaired. In patients with fractured neck of femur, the incidence of deep venous thrombosis is reduced if spinal anaesthesia is used in comparison with general anaesthesia [6]. However, Laaksonen and colleagues [7] failed to find any difference in incidence of deep venous thrombosis between patients having general anaesthesia with spontaneous or controlled ventilation.

Two other features of the anaesthetic methods of the present study might possibly have contributed to the relatively good outcome. In the first place anaesthesia was induced in both groups with etomidate. Because of its cardiovascular stability, this drug may be especially valuable in an elderly population with a significant prevalence of cardiovascular disease and where dehydration is common.

Second, supplementary oxygen was administered continuously to all patients from the end of anaesthesia for at least 6 h. Patients with fractured neck of femur are already relatively hypoxaemic when presenting for surgery [8–10]. Profound decreases in arterial Po_2 may occur if patients are allowed to breathe room air over the first 1 h after general anaesthesia and the lowest values of Po_2 occur between 4 and 8 min after nitrous oxide is discontinued [11]—a period when patients are frequently in transit to the recovery area and seldom receive supplementary oxygen.

Patients in the present study had either dynamic hip screw insertion or primary hip prosthesis. The insertion of prosthesis and cement may be associated with hypotension and hypoxaemia, the latter of which may be unrecognized [12].

It would appear that careful general anaesthesia with avoidance of long acting drugs and with continuous supplementary oxygen in the immediate postoperative period results in a relatively good outcome after surgery for fractured neck of femur, regardless of whether controlled or spontaneous ventilation is used.

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DOUBLE-BLIND, MULTIPLE-DOSE COMPARISON OF BUPRENORPHINE AND MORPHINE IN POSTOPERATIVE PAIN OF CHILDREN

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SUMMARY

In a randomized double-blind study of 57 children (aged 6 months–6 yr), pain following lateral thoracotomy was relieved with repeated i.v. doses of morphine 100 or 50 μg kg^{-1}, or buprenorphine 3.0 or 1.5 μg kg^{-1}. The same drug and dosage were continued and cardioventilatory indices, pain intensity and sedation measured for an observation period of 24 h. The sums of the pain intensity differences were equal in all groups. The mean doses for the complete initial analgesia were 230 and 180 μg kg^{-1} with the larger and the smaller bolus doses of morphine and 5.8 and 3.7 μg kg^{-1} with buprenorphine, respectively. The mean duration of action of buprenorphine was slightly but not significantly longer than that of morphine. The total consumption of both morphine and buprenorphine was less when the smaller bolus doses were used. Two patients developed a degree of ventilatory depression following repeated doses of buprenorphine. Buprenorphine was equal to morphine as a postoperative analgesic.

Pain in childhood is not always managed as actively as that in adults. Studies have suggested that postoperative pain in children is undertreated [1], although even the newborn displays distress in association with surgical stimuli [2].

Antipyretic analgesics given by the rectal route do not relieve severe postoperative pain; narcotic analgesics are required. However, in paediatric practice injections pose a problem because children generally consider them painful. Buprenorphine has been shown to have a longer effect than morphine and to be a useful analgesic in adults [3], and it could thus, theoretically, overcome the problem of frequent injection in paediatric patients. This double-blind multiple-dose study was performed to compare the analgesic efficacy and side-effects of i.v. buprenorphine with those of morphine in the treatment of postthoracotomy pain in infants and young children.

PATIENTS AND METHODS

A randomized double-blind, multiple-dose, noncross-over design, which was accepted by the local ethics committee, was used. The study was undertaken in 60 children, aged 6 months to 6 yr and scheduled for lateral thoracotomy because of coarctation of aorta, patent ductus arteriosus, or lung or other intrathoracic surgery. Patients who had a severe cardiac anomaly, hepatic or renal insufficiency, mental retardation, or required postoperative ventilation were excluded from the study.

For each patient the hospital pharmacy provided the study drug in numbered identical ampoules containing either morphine 10 or 5 mg ml^{-1} or buprenorphine 0.3 or 0.15 mg ml^{-1}. When an analgesic was required, 0.01 ml kg^{-1} of the study drug was administered i.v. (that is, morphine 100 or 50 μg kg^{-1}, buprenorphine 3.0 or 1.5 μg kg^{-1}). No other analgesic was given during the study.

The same premedication and anaesthetic technique were used for all patients. Flunitrazepam was given by mouth for premedication (0.1 mg kg^{-1}, 2 mg maximum). Additional methohexitone

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10–15 mg kg^{-1} was given rectally to infants, if necessary. Before the induction of anaesthesia a standard dose of i.v. atropine was administered. Anaesthesia was induced with thiopentone 3–5 mg kg^{-1} and intubation of the trachea was facilitated with suxamethonium 1.0–1.5 mg kg^{-1}. A maximum of 3 μg kg^{-1} of fentanyl was given at induction or at the beginning of surgery. For maintenance of anaesthesia nitrous oxide in oxygen (2:1) and enflurane were used. Neuromuscular blockade was achieved with pancuronium and the degree of block was monitored with a transcutaneous nerve stimulator. Normocapnia was maintained throughout (Servo 900 ventilator). At the end of surgery any residual neuromuscular blockade was antagonized with standard doses of neostigmine and atropine. The trachea was extubated and the patient transferred to the intensive care unit.

When the patient complained of pain or was judged to have moderate to severe pain, baseline measurements of arterial pressure, heart rate and ventilatory rate, together with pain intensity (PI) and sedation scores, were assessed by specially trained observers. Arterial blood was drawn for blood-gas analysis before the administration of the test analgesic, and once the patient was free of pain. The PI was scored: 0 = no pain; 1–3 = slight pain; 4–5 = moderate pain; 6–8 = severe pain; 9 = worst possible pain. Correspondingly, sedation was scored from 0 to 4 (0 = fully awake; 1 = slightly drowsy; 2 = asleep but easily arousable; 3 = fully asleep but arousable; and 4 = fully asleep, not arousable).

The study drug was given in increments of 0.01 ml kg^{-1} at 5–15 min intervals until the patient was free of pain (PI 0–1 for more than 15 min). After the administration of the study drug the cardioventilatory variables were assessed, together with the pain and sedation scores, at 15-min intervals for 3 h, and additionally at 5 min after the first dose. Thereafter, recordings were obtained hourly. Every time the patient complained of, or was judged to have, moderate to severe pain, the study drug was given in standard doses until the pain was relieved. After these further doses the indices under study were recorded at 15 and 30 min. The observation period was 24 h, during which any side-effects were noted.

Pain intensity differences (PID) and sedation differences (SD) were calculated by subtracting the respective PI values and sedation scores from the pre-drug values. The sum of pain intensity differences (SPID) and the sum of sedation difference scores (SDS) were calculated as the sum of the product of each PID and SD score and the time in hours since the previous observation.

One-way analysis of variance and Student's *t* test for independent samples were used for the statistical analysis of the results.

RESULTS

There were no significant differences between the treatment groups in regard to sex, age, weight, height and the duration of anaesthesia (table I). Pre-drug PI values did not differ (table II). Three patients were excluded from the study: one patient because of the excessive administration of fentanyl during the operation, the second because of undiagnosed neurological disease, and the third

TABLE I. *Characteristics of the different treatment groups. CoA = coarctation of aorta; PDA = patent ductus arteriosus*

Treatment group	Number of patients	Sex (M/F)	Age (yr) (mean ± SD)	Weight (kg) (mean ± SD)	Height (cm) (mean ± SD)	Duration of anaesthesia (min) (mean ± SD)	Type of surgery
Morphine 100 μg kg^{-1}	14	8/6	3.2±2.3	13.2±4.6	93±19	116±35	CoA = 9 PDA = 5 Other = 0
Morphine 50 μg kg^{-1}	14	7/7	2.7±1.9	12.9±4.8	90±18	128±35	CoA = 4 PDA = 3 Other = 7
Buprenorphine 3.0 μg kg^{-1}	15	8/7	2.2±1.2	10.7±3.2	83±12	137±70	CoA = 5 PDA = 7 Other = 3
Buprenorphine 1.5 μg kg^{-1}	14	9/5	3.5±2.3	13.8±5.4	95±20	120±32	CoA = 5 PDA = 5 Other = 4

TABLE II. *Comparison of some specific features of analgesia (mean ± SD). Significant differences from morphine 50 µg kg⁻¹: ns = not significant; *P < 0.05; ***P < 0.005. Significant differences from buprenorphine 1.5 µg kg⁻¹: †P < 0.05; ††P < 0.001 (Student's t test)*

	Morphine groups		Buprenorphine groups		P value of F test
	100 µg kg⁻¹	50 µg kg⁻¹	3.0 µg kg⁻¹	1.5 µg kg⁻¹	
Dose for complete initial analgesia (µg kg⁻¹)	230 ± 139(ns)	180 ± 104	5.8 ± 3.3†	3.7 ± 1.6	—
Time to onset of complete initial analgesia (min)	34 ± 28	63 ± 35	34 ± 24	43 ± 36	0.05
Time to next analgesic after initial pain relief (h)	3.5 ± 3.1	3.0 ± 3.7	4.7 ± 4.1	4.9 ± 3.2	0.42
The second analgesic dose (µg kg⁻¹)	115 ± 36***	74 ± 43	4.0 ± 1.4††	1.6 ± 0.4	—
Drug consumption (µg kg⁻¹ h⁻¹)	41 ± 17*	27 ± 17	1.1 ± 0.5††	0.6 ± 0.2	—
Pre-drug pain intensity (0–9)	5.9 ± 1.5	6.4 ± 0.9	6.3 ± 1.2	6.1 ± 1.2	0.71
SPID	5.3 ± 1.5	5.5 ± 1.1	5.5 ± 1.2	5.3 ± 1.0	0.96
Pre-drug sedation score (0–4)	2.6 ± 1.3	2.1 ± 1.3	1.7 ± 1.5	2.5 ± 1.6	0.62
SDS	0.3 ± 1.2	0.2 ± 1.1	−0.5 ± 1.6	0.2 ± 1.4	0.33

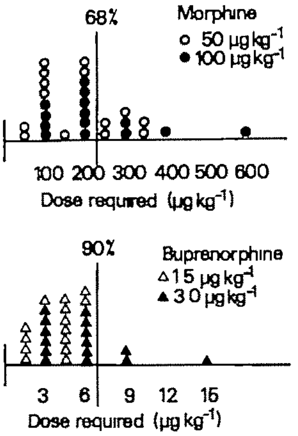

FIG. 1. Distribution of the morphine and buprenorphine doses required to induce complete initial analgesia. The vertical lines and percentages refer to the number of patients completely free of pain at the corresponding doses.

because of a deviation from the design of the study.

The mean doses of morphine (100 and 50 µg kg⁻¹) required to produce complete initial analgesia (PI 0–1) were 230 and 180 µg kg⁻¹, and of buprenorphine (3.0 and 1.5 µg kg⁻¹) 5.8 and 3.7 µg kg⁻¹, respectively (fig. 1, table II). Correspondingly, with the smaller increments of morphine the drug consumption was 27 µg kg⁻¹ h⁻¹. When larger increments were used the dose was 1.5-fold. The mean consumption of buprenorphine was 1.8-fold when larger buprenorphine bolus doses were used. The dose needed to suppress pain seemed to be smaller when smaller bolus doses were used.

Complete initial analgesia was reached in about 34 min when the larger doses of morphine or buprenorphine were used. With the smaller morphine dose, the mean time to the onset of complete analgesia was 63 min. This was significantly ($P < 0.05$) longer than in the other study groups (table II). In the buprenorphine 3.0 µg kg⁻¹ group all patients had reached complete analgesia in 45 min and about 80 % of these remained free of pain for several hours. The other treatments were not equally successful in this respect (fig. 2). The mean duration of action of buprenorphine was approximately 1–2 h longer than that of morphine. However, the differences were not statistically significant.

The mean PI scores of the four treatment groups were the same, indicating that postoperative pain was treated in a similar manner in all groups (fig. 3). With regard to SPID, no significant differences were detected (table II). The potency ratios of buprenorphine to morphine based on various indices are shown in table III.

Both morphine and buprenorphine resulted in marked sedation. There was no significant difference in the SDS values, indicating that approximately similar levels of sedation were achieved.

The pre-drug systolic and diastolic arterial pressures, heart rate and ventilation did not differ between the treatment groups. The decrease in heart rate was insignificant in all treatment groups following the dose which provided complete initial analgesia (fig. 4). The changes in systolic and diastolic arterial pressures were not statistically significant. Only the increase in diastolic pressure after morphine 50 µg kg⁻¹ differed from the other study groups ($P < 0.001$). The changes in the ventilatory rate were not statistically significant.

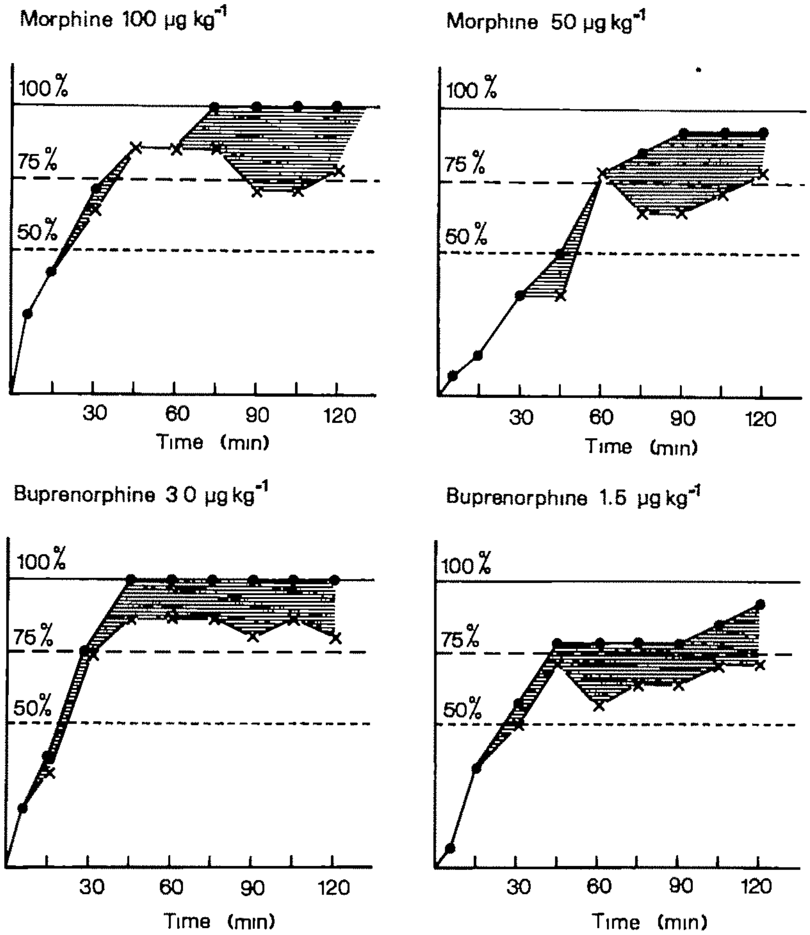

FIG. 2. Percentage of patients with pain intensity (PI) of 0–1 (x) or who have been at a PI level of 0–1 (●) after the administration of morphine or buprenorphine during the first 2 h of the study.

The mean Pa_{CO_2} decreased slightly in all treatment groups when the patients were free of pain compared with the pre-drug value.

The incidence of side-effects was low. Two patients had nausea and vomiting, one in the morphine group and the other in the buprenorphine group. In the buprenorphine group one patient complained of dry mouth and one of itching. Urine retention occurred in one patient in the morphine group. Two patients developed hypoventilation later during the study period following repeated doses of buprenorphine. Complete initial analgesia was achieved with an average dose of buprenorphine in both patients. However,

TABLE III. *Potency ratio for buprenorphine:morphine based on the dose for the complete initial analgesia, the second analgesic dose and the analgesic consumption during the observation time*

	Buprenorphine 3.0 µg kg^{-1} *v*. morphine 100 µg kg^{-1}	Buprenorphine 1.5 µg kg^{-1} *v*. morphine 50 µg kg^{-1}
Dose for the complete initial analgesia	40:1	49:1
The second analgesic dose	29:1	46:1
Drug consumption	37:1	45:1

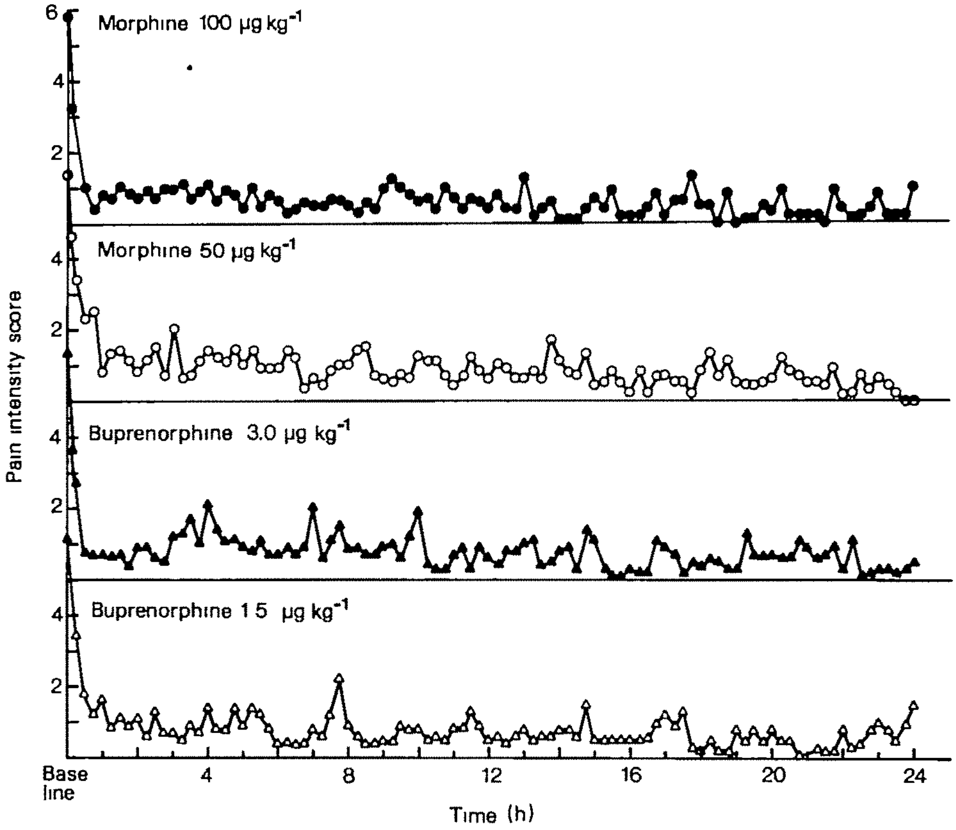

FIG. 3. Mean pain intensity in the four treatment groups.

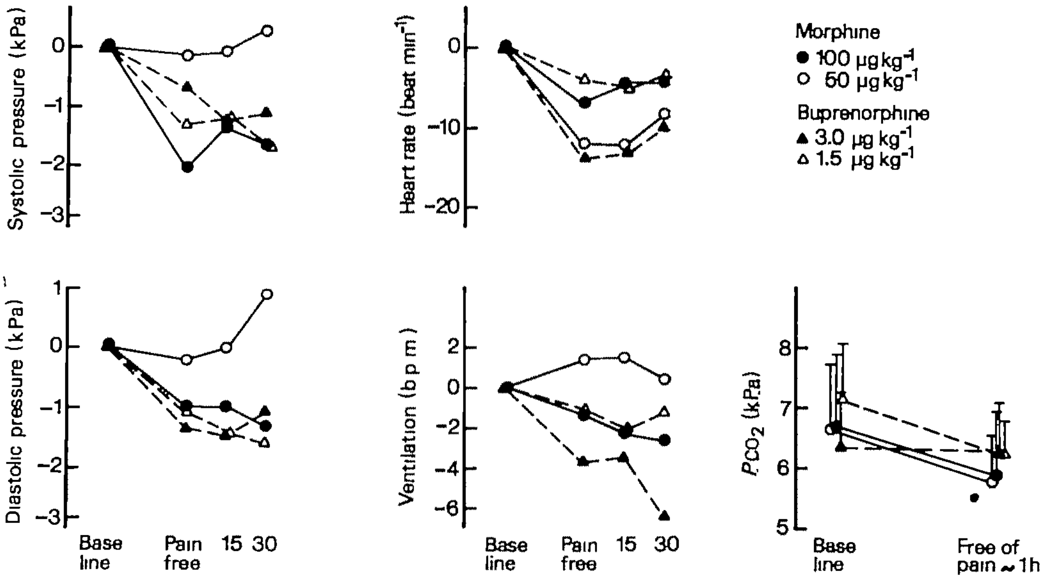

FIG. 4. Mean cardioventilatory changes after the morphine and buprenorphine doses for the complete initial analgesia.

buprenorphine 9.2 μg kg^{-1} was later administered in 4 h to the first, and 6.0 μg kg^{-1} in 2 h to the second patient. The clinical hypoventilation was confirmed with arterial blood-gas analysis in one (Pa_{CO_2} 9.5 kPa) and with measurement of end-expiratory carbon dioxide concentration in the other (9.5 %).

DISCUSSION

The problems associated with the management of pain in children are different from those encountered in the adult. Most children are afraid of i.m. injections because they consider them painful. Although pain in the immediate postoperative period in children can, in many instances, be managed with drugs administered rectally or i.v., the i.m. administration of analgesics may be indicated also. When intermittent injections are given a long duration of action should diminish the number of injections needed and, at least theoretically, be more acceptable to the child. In adults, buprenorphine has been shown to have a long duration of action. Some preliminary studies have shown it to be a promising analgesic in children [4–6]. However, the analgesic effect and side-effects of buprenorphine in multiple doses have not been compared with those of morphine in children.

In the present study a double-blind, multiple-dose study with a relatively long observation period (24 h) was used in order to ensure a reliable comparison between buprenorphine and morphine, both of which were studied in two different bolus doses. The larger dose of morphine (100 μg kg^{-1}) was that used conventionally. The larger dose of buprenorphine (3.0 μg kg^{-1}) is equipotent with morphine 100 μg kg^{-1} [3, 7]. The smaller doses (morphine 50 μg kg^{-1} and buprenorphine 1.5 μg kg^{-1}) were used to establish whether the administration of smaller single doses would offer any advantages over the use of larger doses in the treatment of postoperative pain.

When possible, the subjective assessment of pain should be the primary evaluation. There is, however, a large group of young patients who are incapable of assessing pain verbally or with a visual analogue scale. Therefore, the observer's assessment based on the behaviour of the child is necessary in paediatric practice. The child's reaction to pain is based on his developmental stage. Individuals working with children have to be instructed correctly so as to perform reliably the bedside assessment of pain. We use a 0–9 scale, based on facial expression, vocalization, movements and rigidity of the limbs and body, response to handling, and irritability, together with the measured cardioventilatory indices. The statements of children capable of expressing pain verbally seem to correlate well with the judgement of the observer [8]. In the present study the number of children capable of subjective rating of pain was so low that the subjective pain scores were not included in the assessment.

In the present study the titration to achieve complete initial analgesia was done by a member of the study group. For the rest of the study period the assessments were made by nurses in the intensive care unit who had been instructed to use the method described above. During one shift every assessment of the child was made by the same nurse. The variability in assessments between different nurses was not studied. Because of the long observation period it is probable that the accuracy of the assessment varied. This variability was evenly distributed in the different study groups and probably did not significantly influence the overall assessment of the various indices. The assessments of the complete initial analgesia can be considered very reliable because all the assessments were made by the three members of the study group.

Both morphine and buprenorphine provided good analgesia. The larger dose of buprenorphine seemed to produce complete relief of pain more rapidly than that of morphine. This differs from the previous studies in adults with i.m. drugs [9] and suggests that the current analgesimetric method measures not only pain but also sedation. The variation between individuals of the effective doses of morphine required to produce complete initial analgesia was larger than that of buprenorphine. This might be attributable to the same methodological factors. We have a clinical impression that buprenorphine, in the doses used in the treatment of post-thoracotomy pain, produces more sedation than morphine. In infants and young children the aim of analgesic therapy is to keep the child both free of pain and calm. As only a minority of children in this age group can express their pain verbally, the dosing of analgesic is dependent on the nurse's assessment. As far as young children are concerned, the observer cannot always distinguish sedation from analgesia.

In previous studies in adults the duration of action of buprenorphine has been demonstrated to be considerably longer than that of morphine [3, 10]. In the present study, based on the initial analgesia, the action of buprenorphine lasted somewhat longer than the action of morphine, but there were large interindividual differences. The number of i.v. injections of buprenorphine administered during the observation period was about the same as that of morphine. This suggests that the advantage of the longer action of buprenorphine seems to be limited in paediatric patients. Assuming that the duration of action of buprenorphine and morphine given i.m. to children would be of the same order as that of i.v. administration in the present study, buprenorphine would hardly gain better acceptance among children than morphine.

The effect of buprenorphine on ventilation is controversial. Hovell [11] and Banks [12] have reported that buprenorphine has only minimal effects on ventilation in adults. Others have found that the degree of ventilatory depression after clinical doses of buprenorphine is at least as marked as with morphine [3, 13]. In our study the larger dose (3.0 $\mu g\ kg^{-1}$) of buprenorphine depressed the ventilation rate more than the other analgesics but, based on the arterial blood-gas analysis, none of the analgesics caused hypoventilation consistently. This is in good agreement with our clinical experience. The risk of hypoventilation is minimal when clinically effective doses of narcotics are given for moderate to severe pain in children. In the present study, however, ventilation was depressed in two of the patients treated with buprenorphine. In both, PI was probably misinterpreted. One child had high arterial pressure after the surgical repair of coarctation of the aorta. The nurse gave repeated doses of the study drug (buprenorphine) in order to decrease arterial pressure, which she interpreted being a sign of pain. The other patient was 3 years old and had to remain immobile because of an anterior fixation of the thoracic spine. Every time he woke up, he wanted to take his usual sleeping position. The response of the nurse was to give the study drug. We consider that the overdosage was the result of misinterpretation of the pain score. These two patients do not necessarily reflect the greater potential for ventilatory depression after buprenorphine. However, we doubt if buprenorphine can be considered safer than morphine in children as far as ventilatory effects are concerned.

The incidence of other side-effects was extremely low. According to our clinical experience, this could have been because of the young age of the patients and the type of operation. Obviously, the side-effects of narcotics administered after major surgery are of minor importance in paediatric patients.

Buprenorphine 3.0 and 1.5 $\mu g\ kg^{-1}$ and morphine 100 $\mu g\ kg^{-1}$ for the complete initial analgesia caused similar clinically insignificant changes in arterial pressure and heart rate. The qualitatively different effect of morphine 50 $\mu g\ kg^{-1}$ on these variables was probably a result of the failure of this treatment, when given according to the design of the study, to induce effective and rapid relief of pain. When larger doses of buprenorphine and morphine were used, complete relief of pain was achieved faster. With the smaller bolus doses the complete initial analgesia was not achieved in every patient until the fourth hour of the study. Using larger doses probably caused certain overdosage. This could be responsible for the differences in the dose for the complete initial analgesia, in the second analgesic dose, and in the drug consumption. Probably, the time interval between the analgesic injections was not long enough to allow buprenorphine and morphine to reach their full effect before the next dose was given. The use of smaller bolus doses allowed a more precise titration of the analgesia. However, this did not necessarily improve the comfort of the children.

The potency ratios derived from our results are in agreement with those in earlier studies in adults [3, 7]. The relatively high ratio of buprenorphine to morphine could be attributable to the more sedative effect of buprenorphine being interpreted as better analgesia in young children.

According to our results, buprenorphine was equal to morphine as a postoperative analgesic in children. We could not demonstrate its longer duration of action. The degree of ventilatory depression with buprenorphine was at least as marked as with morphine. Although smaller i.v. bolus doses of morphine and buprenorphine resulted in lower drug consumption, the use of larger doses allowed a more rapid control of pain with no increase in side-effects.

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COMPARISON OF THE EFFECTS OF SUBANAESTHETIC CONCENTRATIONS OF ISOFLURANE OR NITROUS OXIDE IN VOLUNTEERS

I. M. McMENEMIN AND G. D. PARBROOK

SUMMARY

A cross-over trial was performed in 12 volunteers to compare the relative potency of 25% nitrous oxide and 0.4% isoflurane when breathed for a period of 20 min. Oxygen was used as a control. The effects were observed for 35 min after drug administration. Choice reaction time, ability to tap two areas on a board and ability to perform mathematical problems were significantly impaired when inhaling nitrous oxide, the maximum effect being obtained within 5 min. With isoflurane, the effects were significantly greater than with nitrous oxide. The effect obtained after 15 min inhalation was greater than that at 5 min. Tests returned promptly to the base line after the discontinuation of the test agent. Subjective assessments were made using a series of eight visual analogue scales. Results of the scales represented by physical and mental sedation indicated that 0.4% isoflurane was more potent than 25% nitrous oxide. Significant effects were detected up to 15 min after the inhalation of the agent was stopped. Subanaesthetic concentrations of isoflurane warrant further study in patients undergoing dental treatment in which a rapid recovery from sedation is important.

Although nitrous oxide is a useful sedative when used in subanaesthetic concentrations, its specific effects on vitamin B_{12} metabolism and amino acids [1, 2] appear to account for the toxicity to patients associated with its prolonged use. There is also evidence that this toxicity extends to dental staff who regularly administer nitrous oxide [3, 4]. Of alternative agents, subanaesthetic concentrations of trichloroethylene and methoxyflurane have proved less satisfactory because of slowness of uptake and excretion. Isoflurane has a rapid uptake and excretion [5] and should give a controllable level of effect with rapid recovery after use in subanaesthetic concentrations. Furthermore, it undergoes minimal metabolism [5] and long-term use is associated with few after-effects [6] and a lack of toxicity [7, 8]. Consequently, sedation with isoflurane may be expected to be safer than that provided by nitrous oxide, and studies by McLeod and his colleagues [9] have demonstrated the efficacy of isoflurane in patients in labour.

In view of these factors, it was decided to design a trial which compared subanaesthetic concentrations of isoflurane and nitrous oxide in volunteers. Because dentistry appeared one potential field for the clinical use of subanaesthetic concentrations of the agent and since, in our experience, the typical duration of inhalation sedation in dentistry is 20 min, this was chosen as the duration of the inhalation of the agents. For the purposes of the trial, a fixed concentration of 25% nitrous oxide was selected, because this is one which gives proven analgesia and sedation with few side-effects [10, 11]. On the basis of standard minimum alveolar concentrations for anaesthesia, 25% nitrous oxide would be equipotent with 0.3% isoflurane. However, the slower uptake of isoflurane would result in alveolar concentration reaching 60% of inspired concentration at the end of 20 min as opposed to 85% in the case of nitrous oxide. For the purposes of the trial, therefore, an inspired concentration of 0.4% isoflurane was chosen.

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SUBJECTS, MATERIALS AND METHODS

Subjects

Twelve members of the anaesthetic department (7 male) (age range 20–58 yr) volunteered for the study. All were healthy and were taking no medication. Each had the nature of the study explained.

Procedure

Each subject took part in three test sessions, receiving during each 100 % oxygen, 25 % nitrous oxide or 0.4 % isoflurane (the last two in oxygen). Before participating in the formal sessions, each subject was familiarized with the test and gas administration apparatus. Before each session, subjects had refrained from alcohol and coffee for 12 h, and had had a normal night's sleep.

Each session comprised eight series of tests. All sessions took place in the morning, either early or late. Each subject was tested by the same individual and at the same time of day as their previous tests. Each series of tests lasted about 5 min. At 15 and 5 min before the administration of the inhalation agent, two test series were performed, between which a test of mask fitness was obtained. At time 0, the mask was positioned and the appropriate mixture given. A small quantity of strong perfume spray was added to the reservoir bag and connecting tubing with the aim of masking the odour of the vapour. The concentration of isoflurane was increased step-wise from 0.2 to 0.3 to 0.4 % over 1 min. Administration was for 20 min, series of measurements being obtained at 5 and 15 min. Thereafter, the mask was removed and the subject allowed to recover, series of assessments being performed at 25, 35, 45 and 55 min. The order of tests is summarized in table I.

TABLE I. *Scheme of testing sessions*

Time from start of inhalation (min)	Procedure
−15	1st baseline test
−10	Mask fit check
−5	2nd baseline check
0	Start inhalation of gas mixture
5	1st test during inhalation
15	2nd test during inhalation
20	Stop inhalation of gas
25	1st test in recovery phase
35	2nd test in recovery phase
45	3rd test in recovery phase
55	4th test in recovery phase

The order of the administration of the inhalation agent was randomized from the six pairs of possible combinations available from three gases. Neither the subject nor the tester was aware of which gas was being given, this being known only to the anaesthetist giving the mixture (I.M.M. or G.D.P.).

Testing apparatus

Each series of assessments consisted of four tests which were performed in the following order:

Visual analogue scales. Eight different scales were used, the subject being given a sheet of paper on which eight 100-mm lines were drawn with the extremes of each dimension shown at either end. The dimensions chosen are shown in table II and fall into the categories of mental sedation (lines 1 and 2), physical sedation (3 and 4), tranquillity (5 and 6) and mood (7 and 8), as described by Norris [12]. The order of lines on each page was assigned randomly. Subjects were instructed that the terms at the ends of the lines were extremes of feelings and that they should work through each line and place a perpendicular mark—which represented their feelings at that time. The distance from that mark to the left-hand (lines 2, 4, 7 and 8) or right-hand (lines 1, 3, 5 and 6) end of each line was measured in millimetres and recorded.

Choice reaction time. A board similar to that used by Smith and Shirley [13], with 10 lights and corresponding buttons was presented to the subject (fig. 1). From the ready position (central button), the time taken for the subject to move to the button corresponding to whichever light was illuminated by the tester was measured electronically. The tester's choice of light was as-

TABLE II. *Visual analogue lines (not to scale)*

(1)	Alert	________________	Drowsy
(2)	Mentally slow	________________	Quick-witted
(3)	Well co-ordinated	________________	Clumsy
(4)	Lethargic	________________	Energetic
(5)	Excited	________________	Calm
(6)	Tense	________________	Relaxed
(7)	Withdrawn	________________	Sociable
(8)	Depressed	________________	Elated

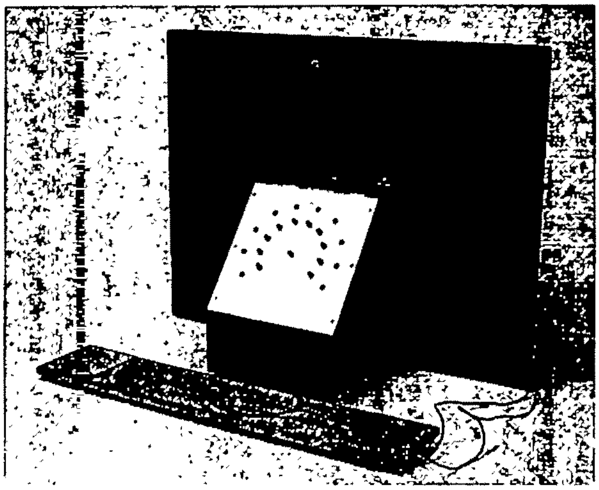

FIG. 1 Choice reaction timer (top) and tapping board used in the study.

signed randomly. Fifteen reaction times were summed and the average recorded.

Tapping board (fig. 1). Subjects were instructed to tap alternately two metal target areas 10 cm × 8.5 cm, set 50 cm apart, as many times as possible in 10 s. Three sessions with 10-s gaps between were performed. The apparatus automatically counted the number of taps over the 10-s session. The total number of taps over the three sessions was recorded.

Mathematical problems. The subject was instructed to complete as many random two-digit addition calculations as possible in 90 s. The number of sums attempted and the number correct were recorded.

Following each test session, subjects were asked which gas they thought they had received; whether the odour of the gas was pleasant, neutral or unpleasant; whether it was acceptable or not; and asked to record any side-effects noted during the inhalation. At a later date, subjects were asked if they experienced any after effects.

Delivery apparatus

A modified Boyle anaesthetic machine was used to deliver the inhalation agent(s), using standard oxygen and nitrous oxide rotameters and a Mark 3 isoflurane vaporizer. To allow delivery of 0.4% isoflurane, a separate oxygen rotameter was installed which bypassed the back-bar of the machine and allowed 10:1 dilution of the mixture passing through the vaporizer, this being set at 4%. Output concentrations were verified by an interference refractometer (Riken). Administration was via an airline pilot's mask, which incorporated a small sampling tube at the expiratory valve, connected to a paramagnetic oxygen analyser (Servomex Ltd) with an attached pen recorder. Oxygen concentration was monitored throughout each session. During the assessment of the fit of the mask, 100% oxygen was given and the fit deemed acceptable if the measured oxygen concentration was greater than 95%. Full resuscitation equipment was available throughout the trial.

Analysis

Numerical data were compared using Freidman's two-way analysis of variance. Pairs of data were then analysed using Wilcoxon Rank Sum test. Statistical significance was deemed to be achieved when $P < 0.05$.

RESULTS

Choice reaction time

Both nitrous oxide and isoflurane decreased reaction time, the effect of isoflurane being greater than that of nitrous oxide (fig. 2). Unlike nitrous oxide, isoflurane did not reach its maximum effect until after 15 min. Within 5 min of stopping the administration, subjects regained values similar to those obtained while breathing oxygen.

Tapping test

An effect similar to that on reaction time was noted, both gases causing a decrease in the number of taps recorded (fig. 3). Again, recovery was noted within 5 min of discontinuation of the inhalation.

Mathematical problems

Both gases decreased significantly the number of sums attempted, isoflurane having a greater effect than nitrous oxide (fig. 4). After 15 min inhalation, the number of sums answered wrongly also increased significantly. No difference was noted once administration stopped.

Visual analogue scales

The effects of the inhalation of nitrous oxide or isoflurane were seen only in the scales rep-

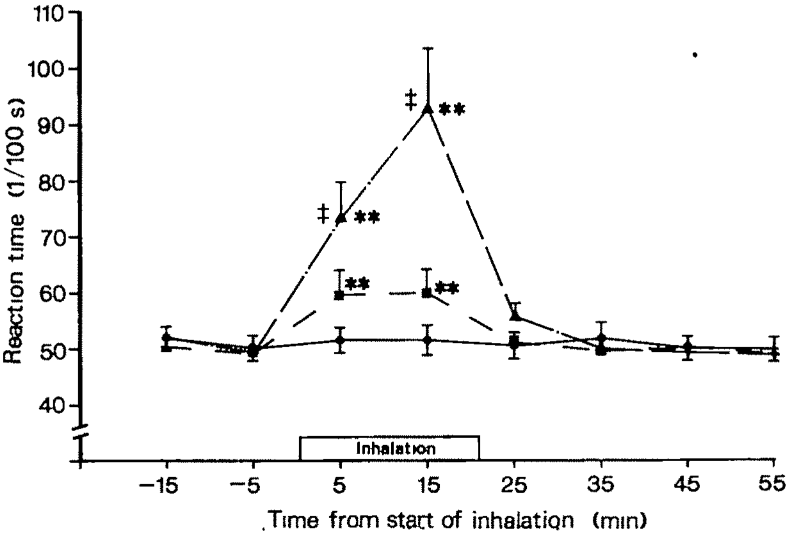

FIG. 2. Mean reaction time (±SEM) before, during and after inhalation of oxygen (●), nitrous oxide (■) and isoflurane (▲). $^{*}P < 0.05$; $^{**}P < 0.01$ = significant difference between nitrous oxide or isoflurane and oxygen; $^{+}P < 0.05$; $^{‡}P < 0.01$ = significant difference between isoflurane and nitrous oxide. Some of the standard errors are omitted for clarity.

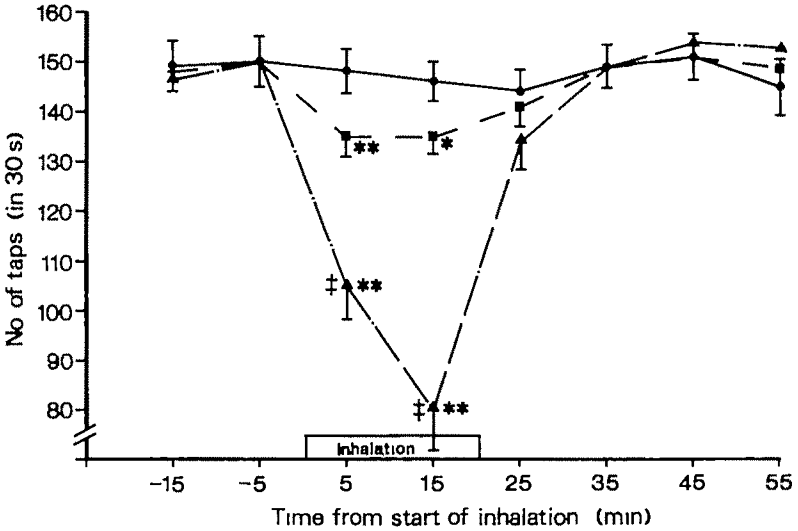

FIG. 3. Mean number of taps (±SEM) before, during and after inhalation of oxygen, nitrous oxide and isoflurane. (For explanation of symbols, see figure 2.)

resenting physical and mental sedation (fig. 5). In contrast to objective testing, this effect continued for 15 min after stopping the inhalation. The effect of the inhalation on feelings of tranquillity was less marked, only isoflurane inducing a feeling of calmness after 5 min (fig. 6). Isoflurane increased feelings of depression compared with nitrous oxide or oxygen after 15 min inhalation. Subjects also felt more withdrawn 5 min after the discontinuation of isoflurane compared with nitrous oxide.

Other effects

The acceptability of the gas and its odour are described in table III. The odour of isoflurane was found significantly more unpleasant compared

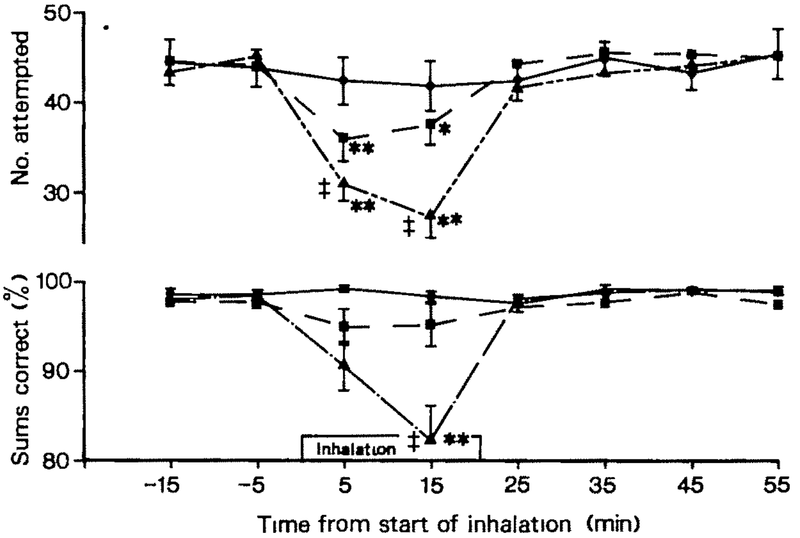

FIG. 4. Mean number of sums attempted and mean percentage correct before, during and after inhalation of oxygen, nitrous oxide and isoflurane. (For explanation of symbols, see figure 2.)

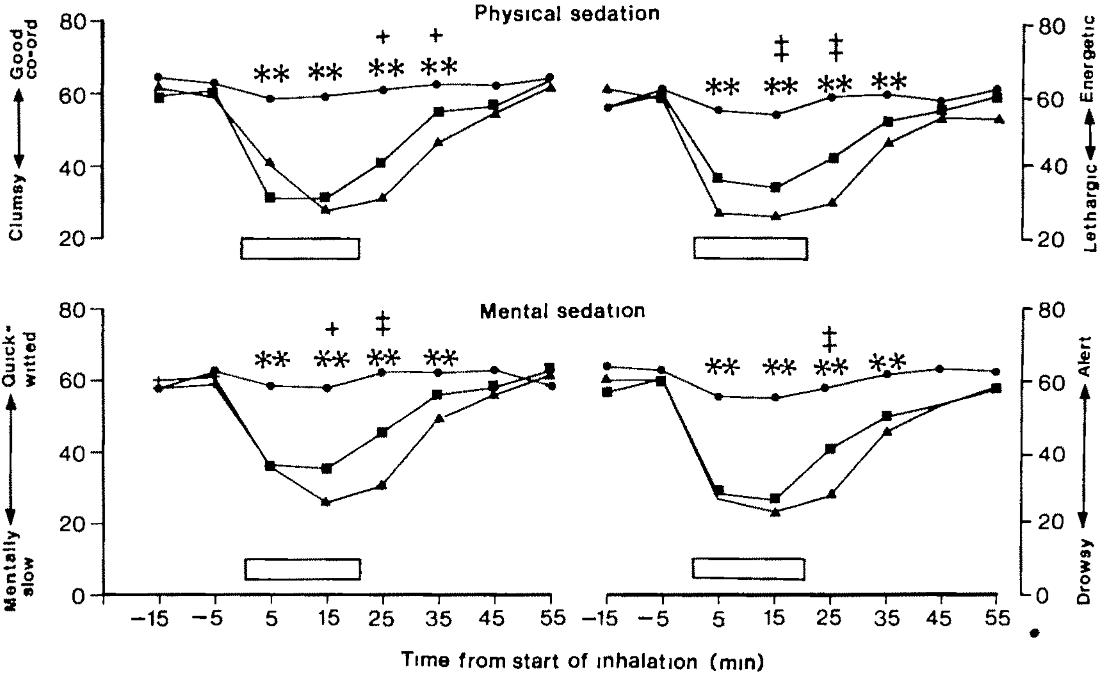

FIG. 5. Mean visual analogue scores representing physical and mental sedation before, during and after breathing oxygen. (●), nitrous oxide (■), and isoflurane (▲). $^{**}P < 0.01$ = difference between anaesthetic gases and oxygen; $^{+}P < 0.05$; $‡P < 0.01$ = difference between isoflurane and nitrous oxide.

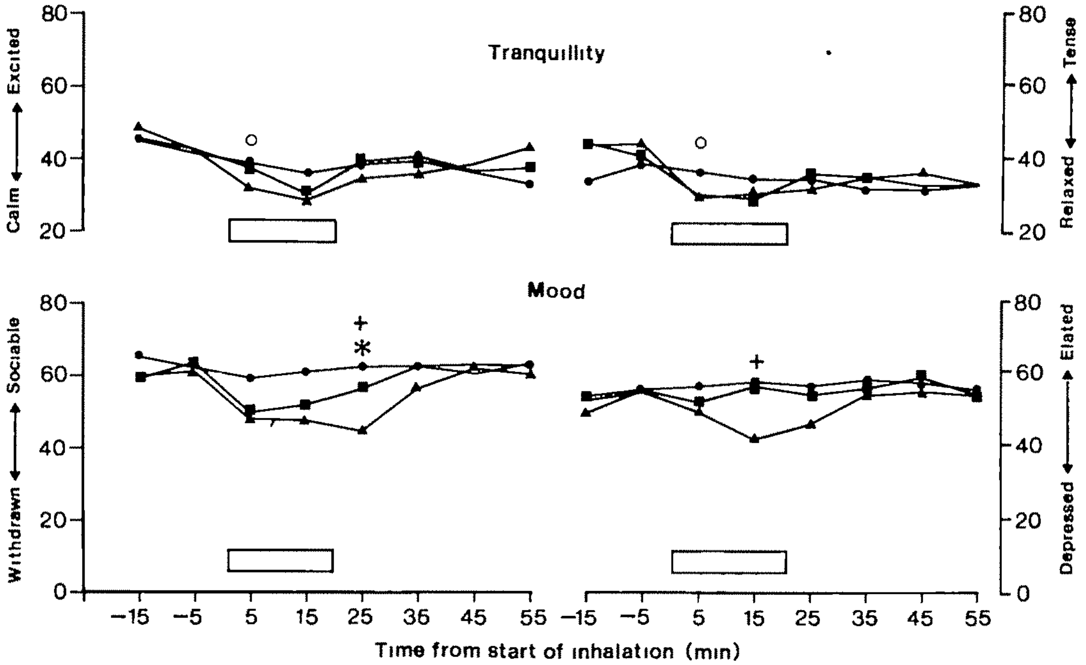

FIG. 6. Mean visual analogue scores representing tranquillity and mood before, during and after inhalation of oxygen, nitrous oxide and isoflurane. °$P < 0.05$ = difference between isoflurane and oxygen; *$P < 0.05$ = difference between anaesthetic gases and oxygen; $^{+}P < 0.05$ = difference between isoflurane and nitrous oxide.

with that of nitrous oxide ($P < 0.05$, Chi-square test), although all but two of the subjects found the gas acceptable. Even with the perfumed spray, 10 of the 12 subjects correctly identified the gas mixture.

TABLE III. *Subject's opinions, and side effects, during and after inhalation of the test gases*

	Inhaled gas		
	Oxygen	Nitrous oxide	Isoflurane
Odour			
Pleasant	1	3	4
Neutral	11	8	2
Unpleasant	—	1	6
Acceptability			
Yes	12	12	10
No	—	—	2
Identification of gas			
Correct	12	10	10
Incorrect •	—	2	2
Side-effects			
Paraesthesia	—	7	1
Nausea	—	1	2
Vomiting	—	—	1

Seven subjects noted paraesthesia while breathing nitrous oxide, only one noting this while breathing isoflurane. Three subjects noted that background noise appeared magnified with nitrous oxide. Two subjects felt nauseated after breathing isoflurane, this continuing for some hours. One of these subjects vomited after the study. Another subject experienced slight nausea while breathing nitrous oxide.

DISCUSSION

The use of a variety of psychomotor tests for the assessment of sedative agents is well established [14]. It is important to choose a test that will give reliable results repeatedly so as to emphasize any differences between sedative agents. Hindmarch [15] and Scott, Whitwam and Wilkinson [16] discussed the effectiveness of a choice reaction timer although, unlike our study, they suggested an analysis of the component parts of the subject's response—processing time (stimulus to start of movement) and movement time. Ghonheim, Mewaldt and Thatcher [17] first described the tapping test and, in conjunction with Kortilla and colleagues [18], found it sensitive both during and after the administration of nitrous oxide. However, in the present study, the effect was slight compared with isoflurane and did not persist into the recovery period.

None of the objective tests demonstrated any marked impairment of function once the administration of the gas had been discontinued. However, the subjective tests demonstrated impairment during the recovery period which was not detected by the objective tests. Subjective tests have been recommended for all such studies [15] and have been discussed at length previously [12, 19]. Clear differences were apparent between the groups expressing mental and physical sedation and those of tranquillity and mood. It may appear anomalous that a gaseous mixture intended for sedation and relief of anxiety did not induce any feelings of tranquillity in the volunteers. However, like Norris [12], who found little effect on the scoring of tranquillity, we are of the opinion that volunteers in familiar surroundings tend to be relaxed and calm initially, drugs making little difference.

Although the inspired concentrations were initially planned to be approximately equipotent in terms of calculated MAC values, the results demonstrated that an inhaled concentration of 0.4% isoflurane gave consistently greater effects than those from 25% nitrous oxide. It is possible that subjects hyperventilated more than anticipated during the trial, to give higher isoflurane alveolar concentrations than expected. Alternatively, the results may represent a real difference in potency at subanaesthetic concentrations. Using similar concentrations, Adams, Castro and Clarke [20] have already demonstrated differences in the amnesic effect of isoflurane, when compared with other anaesthetic agents.

The degree of sedation seen with 0.4% inspired isoflurane was greater than that which would be needed for most clinical procedures and the observers agreed that the volunteers would have fallen asleep had it not been for their will-power in concentrating upon the tests, and the occasional prompting of the supervising anaesthetist.

Despite this degree of sedation, no unpleasant dreams or excitatory phenomena occurred and recovery was prompt, volunteers returning to normal during the afternoon of the study. As was foreseen by Philip [21], and reported by McLeod, Rammayya and Tunstall [9], the smell of the isoflurane was sometimes a problem. Although four volunteers found it pleasant, six found it unpleasant initially and in two of these, the smell persisted throughout the 20 min. One of these volunteers vomited after breathing the anaesthetic. In the case of nitrous oxide too, nausea was seen in one volunteer, even though the 25% concentration used rarely gives any problems in patients. Nausea and vomiting in volunteers may not indicate an equal risk to patients, as Parkhouse and colleagues [22] reported a high incidence of these effects in volunteers receiving nitrous oxide, although similar concentrations have been used in patients without serious problems. For these reasons, and because in practice lower inspired concentrations of isoflurane than 0.4% should suffice, we feel that the smell of isoflurane will not preclude its use in patients and that it will be worthy of clinical trial in patients in whom a period of intense sedation is needed with prompt return to a normal conscious state.

Assessment of the analgesic potency of isoflurane was omitted from these studies as it was felt that the measurement of pain would affect the psychological tests, although other workers have reported that subanaesthetic concentrations of isoflurane produce potent analgesia [9].

In transposing the results of our trial to dental sedation, allowance must be made for air dilution at the Dupaco mask which is commonly used. In dental techniques, 50% air dilution at the mask is common [23]; consequently, the delivered concentrations of an inhaled agent may need to be increased to compensate. In dental sedation techniques, as in others, the concentration of the inhaled agent is usually adjusted according to the patient's response rather than using a fixed concentration as was used in this trial. A preliminary study has been completed and indicates that isoflurane would be of value for sedation in dentistry [24].

In conclusion, isoflurane was an acceptable alternative to nitrous oxide in most of the volunteers. For clinical use, less than 0.4% should be sufficient and a decrease in concentration towards the end of the clinical procedure may be necessary to avoid excess sedation and ensure a more rapid recovery. The problem of nausea and the specific analgesic effect of isoflurane require further study.

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COMPARATIVE *IN VIVO* AND *IN VITRO* ASSESSMENT OF THE PERCUTANEOUS ABSORPTION OF LOCAL ANAESTHETICS

D. F. McCAFFERTY, A. D. WOOLFSON, K. H. McCLELLAND AND V. BOSTON

SUMMARY

The percutaneous absorption of local anaesthetics in a standard formulation has been compared in vitro *and* in vivo. In vitro *data were obtained with a modified Sartorius absorption system and silastic as a lipophilic barrier membrane. With this system the greatest steady-state flux values and permeability coefficients were obtained with amethocaine and lignocaine. These drugs also performed best in an* in vivo *volunteer trial. However, statistical analysis revealed that amethocaine was significantly better at producing full-depth anaesthesia to the challenge of insertion of a sterile needle. An optimized amethocaine formulation may therefore be expected to meet most closely the ideal profile for a percutaneous local anaesthetic preparation.*

The search for clinically effective topical percutaneous local anaesthetic formulations has been undertaken over the past 30 years. It is generally agreed that the ideal formulation should provide rapid, deep and relatively long lasting anaesthesia of both the skin surface and the underlying tissues [1–4]. Percutaneous local anaesthesia is of particular value in paediatric practice. The stress involved on admission of the sick child to hospital has been studied by Blom [5]. Stress can make relatively minor procedures such as venepuncture and insertion of catheters more difficult for both physician and child than is intrinsically necessary [6]. Clearly, there is a need for an anaesthetic preparation which would render such procedures painless. Since infiltration anaesthesia is in itself painful, a topical preparation which allows the anaesthetic to penetrate the skin barrier (stratum corneum) and anaesthetize the underlying pain receptors is required. Additionally, percutaneous local anaesthesia may permit surgical procedures such as split-skin grafting to be undertaken painlessly without the need for general or infiltration anaesthesia.

The stratum corneum is the main barrier to the absorption of drugs through the skin [7]. Thus various percutaneous anaesthetic formulations have been studied for their efficacy at promoting penetration of the barrier by the anaesthetic agent. Unfortunately, these formulations have several disadvantages and, therefore, do not meet the ideal profile for a percutaneous local anaesthetic preparation. For example, dimethylsulphoxide (DMSO) has been used successfully in formulations to enhance the penetration of local anaesthetics, but the adverse side-effects, which were attributed to DMSO, were unacceptable [8, 9]. Although Lubens and colleagues [10] successfuly used lignocaine in a cream base to provide painless venepuncture in children, the drug concentration required was unacceptably high (30 %w/w). More recently, Hallen, Ohlsen and Uppfeldt [4] studied the anaesthetic effect of a gel containing a mixture (5 %w/w) of lignocaine and prilocaine. However, their results indicated that a minimum application period of 1 h (with occlusion) was required to provide adequate anaesthesia.

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Local anaesthetics do not readily penetrate the intact epidermal barrier. It is possible, therefore, that some previous attempts to optimize percutaneous local anaesthetic formulations have been compromised by the inappropriate choice of the actual local anaesthetic agent. In the present study the percutaneous absorption of a number of local anaesthetics is compared both *in vitro* and *in vivo*, with the aim of selecting a suitable drug for development into an optimum formulation.

SUBJECTS, MATERIALS AND METHODS

Chemicals

All materials used were of pharmacopoeal or equivalent quality. Local anaesthetics were in the form of the free base. If the base was not commercially available it was prepared from its water-soluble salt by precipitation with potassium hydroxide 4 mol litre^{-1}. The free base was removed by filtration, recrystallized from an appropriate solvent, washed with water and dried under vacuum. Amylocaine base was an oily liquid and was removed by centrifugation, washed with water and dried over anhydrous magnesium sulphate.

Local anaesthetic formulations

Local anaesthetics (in the form of their free bases) were formulated as oil/water (o/w) creams using emulsifying wax (18%), liquid paraffin (4.5%) and water (77.5%). Formulations were prepared on an equimolar basis to contain in each case 0.035 mol of anaesthetic base per 100 g of cream.

In vitro studies

A modified Sartorius absorption simulator (Sartorius Instruments U.K. Ltd) was used (fig. 1) in conjunction with Silastic MDx-4-4210 (Dow Corning Ltd) as the absorption membrane (0.05 cm thickness, surface area for absorption 15.9 cm^2). The absorption cell was maintained at 32 ± 0.5 °C while the receiving fluid (Ringer's solution) was held at 37 ± 0.5 °C (fig. 1). The receiving fluid (130 ml) was delivered at a rate of 14 ml min^{-1}. The presence of drug in the receiving (sink) phase was monitored spectrophotometrically (Perkin Elmer 554 Spectrophotometer). Concentrations of each drug appearing in the receiving fluid were calculated by reference to a previously prepared calibration curve. Each formulation was run in triplicate.

In vivo studies

These were undertaken on 15 healthy volunteers (9 male) who each gave written informed consent. The study was approved by the University Ethical Committee. The trial for each local anaesthetic formulation was double-blinded using the o/w cream (without anaesthetic) as the control. Application of local anaesthetic/control to the left or right arm was allocated in a random fashion. A minimum period of 7 days was maintained between successive trials on previously treated individuals.

Each formulation was applied (0.5 g) to the ventral surface of the forearm and covered with an Op-Site dressing for 30 min, after which the cream was removed, the site swabbed with 70% alcohol and the area delineated with an indelible marker.

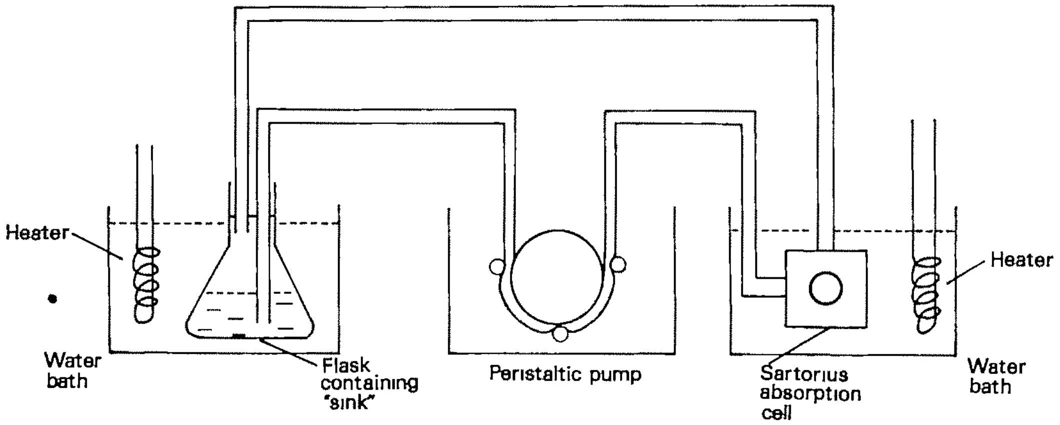

FIG 1. Modified Sartorius *in vitro* absorption system.

Initially, anaesthesia was assessed at 5-min intervals by pricking the skin six times in such a manner as to cover the treated area. If pain was not felt the sterile needle was slowly pushed into the skin until pain was perceived or to a final depth of 9 mm. The depth to which anaesthesia could be detected was graded on a scale 0–2: 0 = no anaesthetic effect; 1 = some depth of anaesthesia was apparent; 2 = anaesthesia of all the layers tested.

Calculation of in vitro *penetration*

The steady-state flux (Q_A) of each anaesthetic across unit membrane area was obtained from the slope of the drug concentration (sink) *v.* time plot via regression analysis of the linear (steady-state) section. The lag times were obtained by extrapolation of the linear plot to the time axis [11].

The permeability coefficient (P) was obtained from:

$$P = Q_A(x/C_0)$$

where C_0 is the concentration of anaesthetic in the donor phase (mg ml^{-1}) and x is the membrane thickness.

Statistical analysis of in vivo *trial*

The percutaneous anaesthetic efficacy of each anaesthetic was assessed against a placebo by means of a chi-square test on a 2 × 2 contingency table. A continuity correction [12] was applied to the calculation of the chi-square statistic, since the numbers in the test were relatively small. A comparison of the efficacy of amethocaine and lignocaine was made by a chi-square test on a 3 × 2 contingency table produced by noting the numbers of volunteers reporting each perceived pain category for these drugs.

RESULTS

In vitro assessment (table I) of the various anaesthetic formulations indicated that penetration of the silastic membrane was dependent on the local anaesthetic used. Penetration efficiency, as judged by the apparent permeability coefficient, was in the order, lignocaine > amethocaine > fomocaine > benzocaine > amylocaine > cinchocaine > mepivacaine > bupivacaine. The last compound showed no penetration through the silastic membrane. The lag time for first appearance of drug in the receptor phase ranged from 18 min for amethocaine to 31 min for mepivacaine.

When the local anaesthetic formulations were tested *in vivo* (table II) the amethocaine formulation showed a 75% success rate, whereas lignocaine was 50% effective in providing percutaneous local anaesthesia. Bupivacaine, cinchocaine and mepivacaine provided no anaesthesia in any of the 15 volunteers.

Statistical analysis of the *in vivo* study indicated that only amethocaine, amylocaine, benzocaine and lignocaine produced a significant anaesthetic effect when compared with placebo (table III).

A statistical comparison of the amethocaine and lignocaine formulations indicated that the former

TABLE I. *Indices of* in vitro *penetration for local anaesthetics*

Anaesthetic	Flux (mg cm^{-2} h^{-1})	Lag time (min)	Permeability coefficient (cm^2 h^{-1} × 10^{-4})
Amethocaine	0.95 ± 0.08	18	5.16
Amylocaine	0.39 ± 0.06	22	2.34
Benzocaine	0.33 ± 0.06	16	2.82
Bupivacaine	0	—	—
Cinchocaine	0.45 ± 0.09	22	1.87
Fomocaine	0.71 ± 0.05	25	3.24
Lignocaine	0.89 ± 0.10	19	5.40
Mepivacaine	0.23 ± 0.03	31	1.34

TABLE II. In vivo *assessment of percutaneous local anaesthesia.* n = *Number of volunteers in whom anaesthesia was evident*

Anaesthetic	*n*	Onset of anaesthesia (min)	Average duration of anaesthesia (min)
Amethocaine	14	41 ± 15	> 90
Amylocaine	8	66 ± 23	39
Benzocaine	8	78 ± 17	23
Bupivacaine	0	—	—
Cinchocaine	0	—	—
Fomocaine	6	75 ± 19	28
Lignocaine	10	70 ± 14	48
Mepivacaine	0	—	—

TABLE III. *Percutaneous anaesthetic efficacy of formulations* v. *placebo*

Anaesthetic	Significance (chi-square)
Amethocaine	$P < 0.01$
Amylocaine	$P < 0.05$
Benzocaine	$P < 0.05$
Fomocaine	$P > 0.1$
Lignocaine	$P < 0.01$

TABLE IV. *Comparison of amethocaine and lignocaine as percutaneous local anaesthetics. 0 = No anaesthesia; 1 = partial anaesthesia; 2 = full-depth anaesthesia. Significance of difference (chi-square)*: $P < 0.01$

	Anaesthetic efficacy		
	0	1	2
No. of volunteers			
Amethocaine	1	2	12
Lignocaine	4	8	3

produced superior percutaneous local anaesthesia, particularly with regard to the depth to which anaesthesia could be obtained (table IV).

DISCUSSION

The purpose of the present study was to attempt to select, on a rational basis, local anaesthetic agent(s) with potential percutaneous local anaesthetic activity. For this reason an initial *in vitro* assessment of the anaesthetic agents was undertaken by examining their penetration of a standard lipophilic membrane.

Silastic (dimethylpolysiloxane) is an isotropic polymer which has been well established for use as a lipophilic membrane with respect to drug absorption [11, 13, 14]. Therefore, it offers a good comparative model of drug penetration by passive diffusion through the skin barrier (stratum corneum) when the lipophilicity of the penetrant is thought to be of prime importance as in the case of local anaesthetics. The Sartorious absorption simulator used for these *in vitro* studies was modified in our laboratory to allow the absorption cell and receiving fluid to be maintained at different temperatures (32 and 37 °C, respectively), thus simulating the *in vivo* situation more closely. A further modification permitted a larger volume of receiving fluid to be used, thus effectively maintaining sink conditions during the course of the investigation. The advantage of using an *in vitro* model is to provide reproducible quantitative data under carefully controlled conditions.

The local anaesthetic agents studied were chosen on the basis of their reported potency, lipophilicity, availability and widespread use. Fomocaine was included because of its reported efficacy as a topical anaesthetic [15]. A standard water-miscible cream formulation was used in all cases for comparative purposes. Each local anaesthetic was formulated on an equimolar rather than an equipotent basis because, in the case of percutaneous absorption, the drug must initially be capable of reaching its target site before exerting an anaesthetic effect. For this reason, differences in drug potencies are virtually irrelevant. Furthermore, drug release from a formulation matrix (cream in the present study) and the establishment of a concentration gradient across a membrane are dependent upon drug concentration; hence, the latter had to be kept constant for each formulation.

It is interesting to observe that all formulations (except bupivacaine which did not penetrate the barrier) exhibited a characteristic lag phase (table I) followed by steady-state permeation of the barrier membrane. It would also appear that the steady-state flux values decrease for different anaesthetics (table I), as the apparent lag time tends to increase. This phenomenon has been previously reported for other drug absorption profiles using various silastic membranes [11]. This lag period can be interpreted as the time required for diffusion of drug molecules into and through the barrier before appearing in the receiving fluid.

It is clear from table I that, of the local anaesthetics examined *in vitro*, the highest apparent steady state flux values obtained were for amethocaine, lignocaine and fomocaine, respectively. A better comparison made on the basis of calculated permeability coefficients (which takes into account the actual drug concentration present in each case) indicates that the efficacy of penetration was in the order lignocaine > amethocaine > fomocaine > benzocaine. Bupivacaine, a potent local anaesthetic, was the most lipophilic agent studied (as determined by the logarithm of the octanol/water partition coefficient, log P), but nevertheless failed to penetrate the silastic barrier. Lignocaine and amethocaine showed similar penetration properties, despite the greater log P value of the latter drug [16]. The low steady-state flux of mepivacaine, however, might have been expected on the basis of its small log P value [16]. A reasonable conclusion from these results is that affinity of the drug for the vehicle is a factor additional to lipophilicity in controlling penetration of the barrier membrane.

Although *in vitro* studies are of use in the design of percutaneous drug absorption systems, they cannot account for the differences in potencies of the various agents studied. Thus, a volunteer trial of the anaesthetic formulations was also carried out. Although a wide variety of stimuli have been used to induce pain, including physical, chemical and electrical methods [17, 18], the simplest and perhaps the most appropriate of these methods involves pricking of the skin with needles [19, 20]. Therefore, the latter technique was chosen as being the most suitable for detecting percutaneous anaesthesia in this study. Initial pin-pricking was followed by insertion of the needle to the skin to mimic venepuncture and to differentiate between surface and full-depth anaesthesia. Also, it can be difficult to reproduce exactly the pin-pricking procedure from one individual to another; hence, the insertion of the needle through the skin was the final test of assessment of anaesthesia. Statistical analysis of the results (table III) indicated that only amethocaine, lignocaine, amylocaine and benzocaine produced a clinical response significantly different from that of placebo. At a higher level of significance ($P = 0.01$) only amethocaine and lignocaine proved better than placebo. Interestingly, these agents also performed best in the *in vitro* study. A detailed comparison between amethocaine and lignocaine (table IV) in terms of their ability to produce full-depth percutaneous local anaesthesia indicated that amethocaine was significantly superior to lignocaine. Although their *in vitro* penetration characteristics were similar, amethocaine has an anaesthetic potency approximately 2.5 times greater than lignocaine [15]. Furthermore, although both drugs had similar lag times *in vitro*, the onset of anaesthesia *in vivo* (measured from the initial time of application) was considerably more rapid, and the average duration of effect longer, with amethocaine than with lignocaine (table II).

Of the other anaesthetics in the study mepivacaine, with an anaesthetic potency similar to lignocaine, had no apparent percutaneous anaesthetic activity (table II), in contrast to a previous report [3]. It did not penetrate the silastic membrane as effectively as some other local anaesthetics. This could possibly be attributed to the fact that the formulation used (alcoholic base) was quite different from that used in this investigation. Furthermore, since these workers used pain stimuli based on electrical stimulation of C fibres and the use of u.v. irradiation, it is possible that the combination of these factors could well explain the different results obtained.

Fomocaine was orginally developed as a highly lipophilic agent designed for topical administration. Although it had a reasonably high flux value in the *in vitro* study, the drug either did not have sufficient potency to produce a complete response *in vivo* or, more likely, it was trapped in the lipophilic membranes of the epidermal layers. The fact that the other local anaesthetics were found to be clinically ineffective was also reflected in the smaller apparent steady-state flux values observed (table I).

The results of the present study indicate that assessment of topical local anaesthetic formulations *in vitro* and *in vivo* identified amethocaine as the most promising percutaneous anaesthetic agent. Since local anaesthetics, as a drug group, do not readily penetrate skin, further work is required to produce an optimum amethocaine formulation which will most closely meet the requirements for an ideal percutaneous local anaesthetic formulation.

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EFFECT OF PASSIVE HYPERVENTILATION ON SEIZURE DURATION IN PATIENTS UNDERGOING ELECTROCONVULSIVE THERAPY

S. N. CHATER AND K. H. SIMPSON

SUMMARY

The influence of end-expired carbon dioxide concentration (E'_{CO_2}) on seizure duration was studied in 30 depressed patients undergoing electroconvulsive therapy (ECT) on three separate consecutive occasions. Unpremedicated patients breathed 100% oxygen before the induction of anaesthesia with methohexitone and the provision of partial neuromuscular blockade with suxamethonium. They then received no further ventilation, 10 breaths, or 20 breaths of hyperventilation with 100% oxygen from a non-rebreathing system with a high fresh gas flow. Transcutaneous oxyhaemoglobin saturation (Sa_{O_2}) was monitored continuously and E'_{CO_2} was measured before and after the seizure. Observation of an isolated forearm was used to time the seizure duration. Sa_{O_2} remained greater than 90% in all patients. Passive hyperventilation with 20 breaths significantly reduced E'_{CO_2} and prolonged seizure duration. E'_{CO_2} before the seizure and change in E'_{CO_2} during the seizure did not correlate significantly with seizure duration.

Electroconvulsive therapy (ECT) is used widely by psychiatrists in the U.K., and there is good evidence of its efficacy in the treatment of depression [1, 2]. Modification of ECT by brief general anaesthesia and partial neuromuscular paralysis has reduced the morbidity associated with the procedure [3]. A bilateral grand mal convulsion must be induced for a therapeutic response to be seen after ECT [4, 5]. When unilateral electrode placement is used it is still necessary to induce a bilateral seizure [5]. A minimum seizure duration may be needed for effective treatment and a single seizure requirement of at least 25–30 s has been suggested [4, 6]. Cumulative seizure durations of 50–400 s using conventional ECT [7] and 210–1000 s during a course of multiple monitored ECT [8] have been proposed. However, the existence of a direct relationship between the efficacy of ECT and seizure duration has been questioned [9,10].

Seizure duration during ECT is dependent on many factors, including concurrent drug therapy [11] and the type and dose of anaesthetic induction agent used [10]. Seizure duration is not dependent on electrode placement, type of stimulating current or electrical energy applied, as long as a supramaximal stimulus is delivered [12]. It was suggested that paralysis and hyperventilation with oxygen resulted in the prolongation of seizure activity [13]. However, it has since been shown that, as long as hypoxaemia is prevented, seizures are not augmented by increasing inspired oxygen concentration alone [14]. Active hyperventilation during the recording of an electroencephalogram enhances epileptiform activity; therefore, hypocapnia may influence seizure activity [15]. In support of this concept, increased seizure duration was seen in association with a decrease in end-expired carbon dioxide concentration (E'_{CO_2}), by full paralysis, intubation and hyperventilation of patients having ECT [14]. The present study was designed to evaluate three different modes of ventilation before the application of an ECT stimulus.

PATIENTS AND METHODS

Thirty patients with major depressive illness (DSM-III criteria [16]) were included in the

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study which was approved by the Hospital Ethical Committee. Patients gave informed verbal consent, and no patient receiving ECT under the provision of the Mental Health Act was involved. Each patient was undergoing a course of bilateral ECT and was studied during three consecutive treatments over a period of 10–14 days. Patients having the first treatment of a course of ECT were not included, as it is known that the duration of seizures is prolonged at this time [5, 17]. Concurrent medication was not altered during the study.

Eight male and 22 female unpremedicated patients aged 31–91 yr, and weighing 30–100 kg, were studied. Before the induction of anaesthesia an earlobe oximeter probe (Ohmeda Biox 3700) was positioned to measure transcutaneous oxyhaemoglobin saturation (Sa_{O_2}) throughout the treatment. Patients were asked to breathe 100% oxygen from an anaesthetic facemask, until Sa_{O_2} 98% was achieved. Anaesthesia was induced with methohexitone 1 mg kg^{-1} and this was followed by suxamethonium 0.5 mg kg^{-1}. The doses of induction agent and neuromuscular blocker remained constant for each patient during the three ECT treatments studied. On each occasion the patients received a different mode of ventilation after induction of anaesthesia and before the application of the ECT electrodes. They received, in randomized order, no further ventilation, or 10 or 20 breaths of hyperventilation with 100% oxygen using a facemask and an oropharygngeal airway. A Mapleson A attachment, modified by replacement of the expiratory valve by an Ambu E valve [18], was used with a fresh gas flow of at least 200 ml kg^{-1}. E'_{CO_2} was sampled through the facemask and measured using a capnograph (Datex Normocap), which was calibrated with a standard gas mixture before and after each session. A pen recorder was used to obtain a record of the E'_{CO_2} immediately before the application of the ECT stimulus, and after the termination of the seizure. Patients did not receive further ventilation between the two recordings of E'_{CO_2}. The ECT stimulus was from the same Ectron Duopulse machine, the output of which was tested before each treatment session. Bifrontotemporal electrodes were applied in a standard position by the psychiatrist, after thorough degreasing of the skin. A bilateral 3-s constant current (850 mA), unidirectional 50-Hz sine wave was used, which delivered 33 J. Seizure duration was timed by observation of the isolated forearm as described by Fink and Johnson [6].

The results were analysed using linear regression and analysis of variance for correlated means, followed by the Tukey test, where appropriate.

RESULTS

Sa_{O_2} did not decrease to less than 90% in any patient, at any time, during anaesthesia or the seizure. Ten or 20 breaths before the application of the ECT stimulus significantly reduced mean E'_{CO_2} compared with no ventilation ($f = 40.73$, $P < 0.01$) (table I). Mean E'_{CO_2} was significantly greater after the seizure when the patients received no ventilation before the shock compared with those occasions when they received 10 breaths ($f = 5.68$, $P < 0.05$) or 20 breaths ($f = 5.68$, $P < 0.01$) (table I). Mean seizure duration was significantly increased when the patients received 20 breaths, compared with those occasions on which they received 10 breaths or no further ventilation ($f = 11.57$, $P < 0.01$) (table I). There was sig-

TABLE I. *Mean (95% confidence interval) end-expired carbon dioxide concentration (E'_{CO_2}) before and after the seizure, and seizure duration, associated with the three different ventilation regimens.* † *Less than no ventilation ($P < 0.01$);* **greater than 10 ($P < 0.05$) and 20 ($P < 0.01$) breaths;* ***longer than no ventilation and 10 breaths ($P < 0.01$)*

	No ventilation	10 breaths ventilation	20 breaths ventilation
E'_{CO_2} before seizure (%)	4.95 (4.75–5.15)	4.38† (4.01–4.75)	3.86† (3.49–4.23)
E'_{CO_2} after seizure (%)	5.80* (5.47–6.13)	5.40 (5.09–5.71)	5.25 (4.94–5.56)
Seizure duration (s)	30.3 (25.8–34.5)	32.4 (27.7–37.1)	36.8** (32.7–40.9)

nificant between-subjects variation in seizure duration ($f = 10.90$, $P < 0.01$).

Analysis of variance of the change in seizure duration (duration after 20 breaths minus duration after no further ventilation) did not reveal significant between-subjects variation ($f = 2.77$, ns). There was no significant correlation between E'_{CO_2} before the seizure and the seizure duration. There was no significant correlation between the change in E'_{CO_2} during the seizure and seizure duration.

DISCUSSION

Twenty breaths of passive hyperventilation with 100% oxygen, using a facemask and non-rebreathing system, reduced E'_{CO_2} and prolonged seizure duration in patients undergoing ECT. The anaesthetic technique was simple and could be used routinely. Bergsholm, Gran and Bleie [14] described an anaesthetic technique involving prolonged neuromuscular blockade and tracheal intubation; however, this could not be incorporated readily to clinical practice in the U.K.

Concurrent medication was not altered and patients acted as their own controls during the present study, to limit the effects of drug treatment on seizure duration. Hypoxaemia may occur during routine ECT treatment [19], and may play a role in limiting seizure duration [20]. Measurement of Sa_{O_2} in the present study excluded hypoxaemia as a factor affecting seizure duration. Preoxygenation to achieve Sa_{O_2} 98% ensured that hypoxaemia did not occur during treatment, even when patients received no further ventilation. Preoxygenation could, therefore, be used to prevent hypoxaemia in patients in whom it is deemed necessary to avoid passive ventilation, but monitoring of oxygen saturation is still desirable.

Considerable variation in seizure duration between individuals has been documented previously [8] and was apparent in the present study. The lack of correlation between E'_{CO_2} before a seizure and seizure duration may be explained by individual variation in seizure duration. The lack of between-subjects variation in change in seizure duration, after 0 or 20 breaths, suggests that the effect of hyperventilation on seizure duration was consistent. The increase in E'_{CO_2} seen during the seizure did not correlate with its duration, perhaps because carbon dioxide production is dependent on muscle activity as well as the duration of apnoea. Although the duration of each seizure was measured, it was not possible to grade the intensity accurately.

In conclusion, passive hyperventilation using 20 breaths of 100% oxygen significantly prolonged seizure duration in patients undergoing ECT, and could easily be incorporated to current clinical practice.

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EFFECTS OF ATRACURIUM, VECURONIUM OR PANCURONIUM PRETREATMENT ON LIGNOCAINE SEIZURE THRESHOLDS IN CATS

W. L. LANIER, F. W. SHARBROUGH AND J. D. MICHENFELDER

SUMMARY

Among the non-depolarizing neuromuscular blocking drugs, atracurium appears to be unique in its ability to produce cerebral stimulation in lightly anaesthetized animals. This effect is attributed to the atracurium metabolite, laudanosine. The following studies were performed to determine if pretreatments with the non-depolarizing neuromuscular blockers pancuronium, atracurium or vecuronium would differ in their effects on the seizure threshold of lignocaine. Adult mongrel cats were anaesthetized with 1.0 MAC halothane in oxygen and nitrogen. Ventilation, blood-gas tensions, acid–base balance and temperature were controlled. Cats received pancuronium 0.2 mg kg^{-1} i.v. (n = 7), atracurium 1.0 mg kg^{-1} i.v. (n = 7) or vecuronium 0.2 mg kg^{-1} i.v. (n = 7). Ten minutes after the administration of the myoneural blocker, all cats received lignocaine 4 mg kg^{-1} min^{-1} i.v. until the onset of EEG evidence of generalized seizure activity. At seizure onset, there were no statistically significant differences among the cumulative lignocaine doses or the serum lignocaine concentrations in cats pretreated with pancuronium, atracurium or vecuronium.

Neuromuscular blocking drugs are large, charged molecules which do not readily cross the blood–brain barrier [1–3]; however, cerebral effects of i.v. administered depolarizing and non-depolarizing myoneural blockers have been reported. In general, when neuromuscular blocking drugs are given to lightly anaesthetized subjects, depolarizing drugs tend to produce cerebral stimulation, while non-depolarizing drugs tend to depress cerebral function. This depression of cerebral function by non-depolarizing neuromuscular blockers has been manifested as EEG synchronization following i.v. gallamine [4] and as a reduction in the minimum alveolar anaesthetic concentration (MAC) in man following i.v. pancuronium [5]. Although the cerebral effects of vecuronium are not as thoroughly defined as those of many of the other commonly used drugs, vecuronium would be expected to affect cerebral function in a manner similar to pancuronium. Both myoneural blockers produce a non-depolarizing blockade, while neither has cerebral-active metabolites or an effect on circulating histamine, all of which are proposed mechanisms whereby myoneural blocking drugs may affect cerebral function [6].

In contrast to the effects of other non-depolarizing neuromuscular blocking drugs, atracurium, when given in large i.v. doses (1.0 mg kg^{-1}) to lightly anaesthetized dogs, produces EEG arousal [6]. This arousal response has been attributed to the atracurium metabolite laudanosine [6], a known cerebral stimulant [7] and seizure-producing agent [8, 9]. It is unknown if the cerebral stimulating effects of atracurium, as demonstrated by the EEG, correlate with alterations in seizure thresholds of any origin.

Generalized seizure activity is a well appreciated complication of excessive local anaesthetic administration, including the local anaesthetic lignocaine [10]. Furthermore, neuromuscular blocking drugs may be used in many patients in whom lignocaine is used for the induction of a regional anaesthetic technique, as

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an i.v. general anaesthetic supplement, or as an antiarrhythmic agent. Previous studies have demonstrated that the seizure threshold of lignocaine may be altered by gallamine [11] and suxamethonium [12]. The effects of pancuronium, vecuronium and atracurium on the lignocaine seizure threshold have not been reported.

The following study was designed to test the hypothesis that, since EEG evidence of cerebral arousal following i.v. atracurium differs uniquely from the cerebral response to other non-depolarizing myoneural blocking drugs, atracurium will also differ in its effect on lignocaine-seizure thresholds when compared with pancuronium and vecuronium.

MATERIALS AND METHODS

Formal approval for these studies was obtained from the Institutional Animal Care and Use Committee. Subjects were 21 unmedicated mongrel cats weighing 3.7 ± 0.2 kg (mean ± SEM). Anaesthesia was induced with 3% inspired halothane in oxygen, and the trachea was intubated without the use of a neuromuscular blocking drug. Anaesthesia was maintained with 1.5% inspired halothane in 30–40% oxygen and nitrogen during the preparatory period. Ventilation was controlled with a Harvard ventilator and adjusted along with the inspired oxygen concentration to maintain control values of blood-gas tensions (Instrumentation Laboratory, Inc. electrodes at 37 °C) at Pa_{O_2} 20.3 ± 0.3 kPa (mean ± SEM) and Pa_{CO_2} 4.7 ± 0.0 kPa. Cannulae were placed in a femoral artery for continuous pressure measurements and blood sampling, and in femoral and forelimb veins for fluid and drug administration. During the preparatory period, cats were given i.v. infusions of lactated Ringer's solution 10 ± 3 ml kg^{-1} (two cats in each group) or 5% dextrose in lactated Ringer's solution 7 ± 1 ml kg^{-1} (five cats in each group). Sodium bicarbonate was given i.v., if needed, to maintain the buffer base (BB+) around 40 mmol $litre^{-1}$. Since the infusions of lignocaine decreased mean arterial pressure (MAP) during the study period, phenylephrine 0.04 mg ml^{-1} i.v. was used in 20 of 21 cats to maintain MAP $\geqslant$ 60 mm Hg. Rectal temperature was measured with a thermistor and maintained near 38 °C with heating lamps and pads. Inspired and end-expired halothane concentrations were measured with an infra-red analyser calibrated for halothane (Beckman Medical Gas Analyser LB-2). Heart rate (HR) was determined from a lead II ECG which was continuously recorded using skin needle electrodes. A six-lead, three-channel bi-frontal, bi-parietal, and bi-occipital EEG was recorded from gold electrodes glued to the calvarium. A 10-kΩ "dummy" circuit was also recorded to detect electrical artefacts. Electroencephalographic filter settings were such that the linear frequency response range was between 1 and 70 Hz.

Fifteen minutes before the definitive study period, the halothane concentration was decreased to 0.83 ± 0.00% end-expired (1.0 MAC). The cats were then divided into three groups and, over a 1-min period, given i.v. infusions of atracurium 1.0 mg kg^{-1} ($n = 7$), pancuronium 0.2 mg kg^{-1} ($n = 7$), or vecuronium 0.2 mg kg^{-1} ($n = 7$). These doses were chosen to represent twice the intubating dose of the various drugs in man. Ten minutes after the completion of the administration, lignocaine hydrochloride 4 mg kg^{-1} min^{-1} in 0.9% saline solution 3.6 ml min^{-1} was infused to a forelimb vein at a Y-piece to which an additional "flush" of 0.9% saline solution was infused. The flush solution was begun at a rate of 3.6 ml min^{-1} before the lignocaine infusion and continued for 30 s after the cessation of the lignocaine infusion. Assuming the pharmacokinetics of atracurium and its metabolite laudanosine are similar in cats, dogs and man [13, 14], this sequence of neuromuscular blocker followed in 10 min by lignocaine would produce near maximum increases in brain laudanosine concentration at the time of seizure onset [6].

EEG activity was recorded before and during the infusion of the myoneural blocker, and at 2.5, 5.0 and 7.5 min after the infusion; and continuously, beginning 1 min before the infusion of lignocaine until the end of the study.

Since all study subjects were paralysed, it was necessary to define seizure onset using EEG criteria. The infusion of lignocaine was discontinued with the onset of seizure activity, which was defined as the appearance of electrical attenuation in all three EEG leads $\geqslant$ 1.0 s followed by polyspike or polyspike and wave activity (fig. 1). These criteria were determined by observing the most frequent seizure pattern that was readily reproducible and easily recognized prospectively in real time as determined by pilot studies. The EEG criteria used to define the onset of seizure activity were similar to those used in previous studies [12, 15, 16].

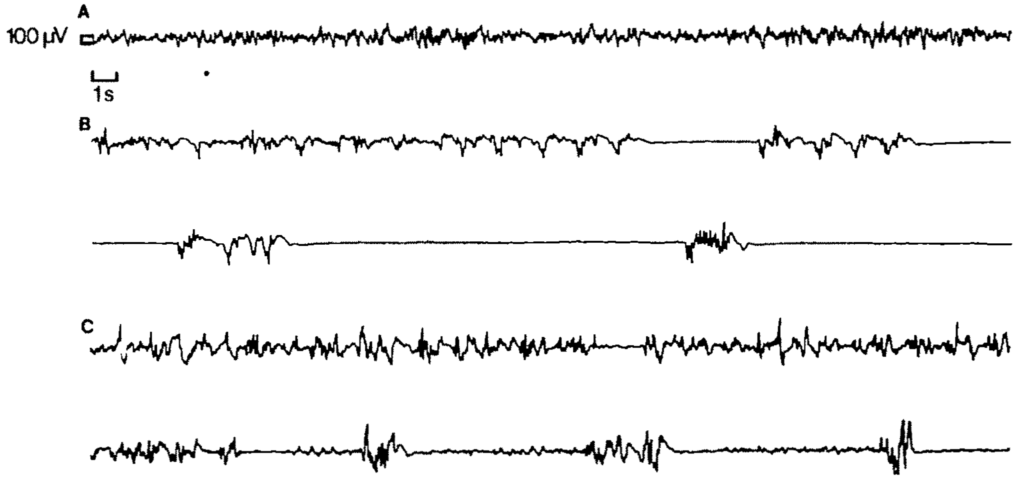

FIG. 1. The pre-lignocaine control EEG (A) was typical of an "anaesthetic" pattern [6] in all cats, both before and after administration of the neuromuscular blocking drug. The predominant EEG rhythm was of 4–6 Hz, 150–300 µV rhythmic theta activity, while individual cats had superimposed rhythms of 10–14 Hz, 60–120 µV rhythmic fast activity, intermittent high voltage delta activity (2–4 Hz, 200–400 µV), or both. Consistent with previous reports [30], lignocaine infusion initially produced an increase in EEG amplitude and a decrease in frequency, typical of increasing anaesthetic depth, until evidence of seizure activity was noted. The seizure "marker" used to determine seizure threshold in the current study was defined as the complex of electrical attentuation of ⩾ 1.0 s followed by polyspike or polyspike and wave activity (B and C). EEG attenuation between periods of polyspike activity frequently resembled the isoelectric or "flat" EEG (B), as has been previously described [12, 17]. However, in other cats during the periods of attenuation there was low amplitude activity (C) which was clearly distinguishable from both electrical artefact and polyspike and wave activity. All of the above recordings are from biparietal electrodes.

An attempt was made to compare seizure thresholds in treated cats with those in unparalysed, placebo-treated cats; however, this was not technically possible. During the infusion of lignocaine in unparalysed cats in pilot studies, muscle twitching often preceeded EEG evidence of seizures. This phenomenon has been described previously in man [17]. The lignocaine-induced muscle twitching, along with ocular and lingual movements, produced EEG artefacts which made accurate assessment of the onset of seizure activity impossible using electrodes glued to the calvarium.

Arterial blood samples that would be used for blood-gas analysis and serum lignocaine determinations were drawn at the the time of the onset of seizure activity in all cats. Samples for the measurement of serum lignocaine concentration were frozen at −70 °C until analysed using an enzyme immunoassay technique (EMIT: Syva Company, Palo Alto) [18]. All samples were serially diluted until dilutions were obtained which provided EMIT measurements within the 0–12-µg ml^{-1} calibration standards. This methodology has a reported coefficient of variation of 3.4%, and results from this technique correlate well with values obtained by gas–liquid chromatography ($r = 0.976$) [18]. At the completion of study, cats were killed with i.v. potassium chloride, and the isoelectric EEG was evaluated for artefacts. Retrospective EEG analysis was performed by a blinded observer (F.W.S.).

Comparison of data was made using paired t tests and Bonferroni's correction of unpaired t tests. $P < 0.05$ was considered significant when comparing paired data, and, because multiple comparisons were made, a Bonferroni's corrected P value of $0.05/3 = < 0.016$ was considered significant when comparing unpaired data. The correlation between the duration of the lignocaine infusion and serum lignocaine concentration was assessed by determining the Pearson product–moment correlation coefficient. Data are presented as the mean ± SEM.

RESULTS

Values for physiological variables during the control period and at the onset of seizures are listed in table I. There were no significant

TABLE I. *Systemic variables (mean ± SEM) during the control period and at seizure onset.* n = *7 for all groups.* **Significantly different from control value* ($P < 0.05$). *There were no significant differences among study groups during either measurement period*

	Control			Seizure onset		
	Atracurium	Vecuronium	Pancuronium	Atracurium	Vecuronium	Pancuronium
Wt (kg)	3.6±0.2	3.5±0.3	4.0±0.4	—	—	—
Pa_{O_2} (kPa)	20.4±0.4	20.3±0.5	20.0±0.5	20.5±0.5	21.6±0.8	20.8±0.9
Pa_{CO_2} (kPa)	4.5±0	4.7±0.1	4.7±0.0	4.4±0.3	4.7±0.1	4.4±0.3
pH	7.38±0.01	7.37±0.02	7.37±0.01	7.36±0.02	7.35±0.02	7.36±0.02
BB+ (mmol litre^{-1})	42±0	41±1	41±1	40±0*	40±1	40±1
Haematocrit (%)	27±2	28±1	27±1	—	—	—
Rectal temp. (°C)	37.9±0.1	38.0±0.1	37.9±0.1	37.9±0.1	37.8±0.0*	37.9±0.1
MAP (mm Hg)	121±5	129±8	123±6	103±7	91±7*	89±7*
HR (beat min^{-1})	186±14	174±17	196±14	129±7*	138±10	123±10*
Expired halothane (%)	0.83±0.00	0.83±0.00	0.83±0.01	0.84±0.01	0.84±0.00	0.84±0.01
Serum lignocaine (μg ml^{-1})	—	—	—	42.1±4.8	47.6±5.2	68.2±11.6
Duration of lignocaine infusion (s)	—	—	—	235±21	284±14	258±20
Cumulative lignocaine dose (mg kg^{-1})	—	—	—	15.7±1.5	19.0±1.0	17.2±1.4

differences among groups at either measurement period. Infusion of the various neuromuscular blocking drugs during 1.0 MAC halothane anaesthesia had no apparent independent effect on the EEG.

At seizure onset, several variables had changed from control values by quantities that were physiologically acceptable but statistically significant. Mean arterial pressure and HR tended to decrease in all groups; however, the changes in MAP were significant only in pancuronium- and vecuronium-treated cats, while the decreases in HR were significantly different only in atracurium- and pancuronium-treated cats. A decrease in BB+ of 2 mmol litre^{-1} in atracurium-treated cats and a mean decrease in temperature of 0.2 °C in vecuronium-treated cats were both statistically significant.

Serum lignocaine concentrations obtained at the onset of seizure activity did not significantly differ among groups of cats pretreated with atracurium 42.1±4.8 μg ml^{-1}, pancuronium 68.2 ±11.6 μg ml^{-1} or vecuronium 47.6±5.2 μg ml^{-1}. The mean cumulative lignocaine dose at the onset of seizure activity for all cats was 17.3±0.8 mg kg^{-1} and did not differ significantly among the groups (table I). There were no significant differences among the groups regarding the durations of lignocaine infusions (table I), and there was no meaningful correlation between the durations of the infusions of lignocaine and measured serum lignocaine concentrations ($r = -0.03$, $P > 0.8$) (fig. 2). Mean phenylephrine dose for all cats was 0.16±0.04 mg and did not significantly differ among groups.

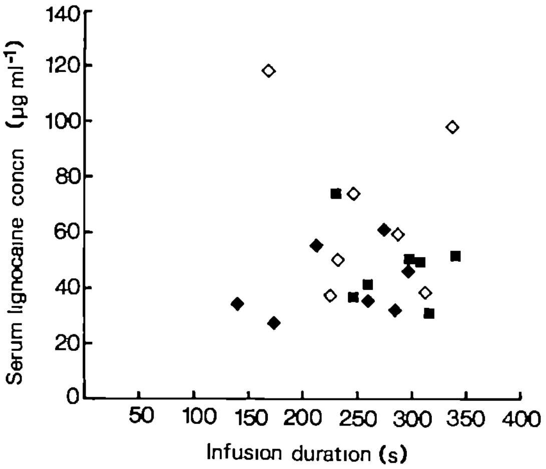

FIG. 2. The relationship between the durations of the lignocaine infusion and serum lignocaine concentrations. There was no meaningful correlation between the durations of lignocaine infusions—and thus cumulative lignocaine doses—*v.* the measured serum lignocaine concentrations ($r = -0.03$; $P > 0.8$). ◆ = Atracurium; ◇ = pancuronium; ■ = vecuronium.

DISCUSSION

Neuromuscular blocking drugs are large charged molecules that are reported either not to cross the blood–brain barrier [2, 3] or to cross the blood–

brain barrier in limited amounts [1]. In spite of these considerations, alterations in cerebral function following the i.v. administration of neuromuscular blocking drugs are well documented. Theoretically, the induced changes in cerebral function may alter the lignocaine seizure threshold either by modifying cerebral function in a manner that is additive with the effects of lignocaine, or by altering cerebral blood flow so that the distribution of lignocaine is changed. These alterations in cerebral function can be attributed to four extracerebral mechanisms: changes in afferent muscle activity induced by the myoneural blocking drug; release of cerebral-active metabolites; histamine release; and alterations in Pa_{CO_2}.

The afferentation theory of cerebral arousal predicts that agents or manoeuvres that actively or passively cause muscle stretch or contraction or stimulate afferent muscle spindles will stimulate the brain [19–21]. Agents that inhibit muscle stretch or contraction may decrease cerebral activity [4, 5]. Induction of depolarizing neuromuscular blockade by suxamethonium, decamethonium and carbolonium have been shown to induce EEG arousal [19, 20]. With suxamethonium, this EEG arousal is accompanied by increases in cerebral blood flow [21]. In contrast, gallamine-induced non-depolarizing neuromuscular blockade produces electrocortical synchronization in cats [4], and pancuronium exerts an anaesthesia augmenting effect in halothane-anaesthetized man [5].

The afferentation theory probably best explains previous reports of the influence of gallamine and suxamethonium on lignocaine seizures. Gallamine has no known effect on cerebral blood flow, yet gallamine-induced non-depolarizing neuromuscular blockade increases the lignocaine seizure threshold in monkeys [11]. We must assume that the gallamine-induced alterations in seizure threshold are the result of some functional interaction between lignocaine and gallamine-induced cerebral electrical depression [4]. In contrast to the increase in lignocaine seizure threshold produced by gallamine, suxamethonium-induced depolarizing neuromuscular blockade decreases the lignocaine seizure threshold in cats [12]. It is unclear whether this effect is the result of a functional interaction between suxamethonium and lignocaine, or whether the seizure threshold decrease was the result of an increase in cerebral blood flow following suxamethonium [21]. All three blocking drugs used in the current study produced complete non-depolarizing neuromuscular blockade, and their effects on cerebral function, as predicted by the afferentation theory, should not differ.

Contrary to the cerebral effects of non-depolarizing drugs predicted by the afferentation theory, atracurium in large doses (1.0 mg kg^{-1}) produced EEG arousal in dogs receiving sub-MAC concentrations of halothane [6]. This arousal response has been attributed to the metabolite laudanosine, a known cerebral stimulant [7] and seizure-producing agent [8, 9]. Although the production of laudanosine by clinical doses of atracurium is much less than the laudanosine doses previously reported to produce seizures in animals [6], we hypothesized that the atracurium-induced production of laudanosine might be sufficient to alter the lignocaine seizure threshold. The current data do not support that hypothesis.

The release of histamine induced by certain myoneural blockers may also affect cerebral function and influence the amount of lignocaine required to induce seizures. Histamine is a direct cerebral vasodilator producing increases in cerebral blood flow [22], and there is some evidence that histamine has a stimulating effect on cerebral electrical activity [23]. In addition, histamine can produce increases in Pa_{CO_2} secondary to an increase in pulmonary deadspace [24], and increases in Pa_{CO_2} can in turn produce increases in cerebral blood flow [25] and cerebral electrical excitation [26]. Atracurium is reported to release histamine in approximately one-third the amount noted following the administration of tubocurarine [27], while pancuronium and vecuronium do not readily release histamine [28, 29]. Despite histamine release after atracurium, we recently demonstrated no significant alterations in CBF in dogs given massive doses of either atracurium or pancuronium during 1.0 MAC halothane anaesthesia [6]. There were no significant alterations in Pa_{CO_2} during the present study, so we can discount histamine-induced carbon dioxide-mediated cerebral effects following atracurium; however, our study design would not eliminate any direct histamine-induced effects on either CBF or cerebral electrical activity.

In the present study, we elected to administer lignocaine as a continuous infusion until the onset of seizures, as has previously been reported [11, 17, 30]. Since lignocaine acts as a general anaesthetic at subconvulsant doses [31], this methodology resulted in an initial synchronization of the EEG as has previously been reported [30], followed by the onset of isolated spikes that were difficult to distinguish from background activity, followed by the combination of polyspike or polyspike and wave activity and electrical attenuation. The latter was used as the seizure "marker" in this study, for it was readily identifiable in real time, was similar to the marker used in previous reports, and is reported to coincide with the onset of tonic–clonic muscle activity in cats [12, 15, 16, 32].

The definition of seizure threshold in previous studies using infusions of lignocaine has been described in terms of the cumulative dose of lignocaine given at the onset of seizures [17, 30] or the plasma lignocaine concentrations measured at the onset of seizure activity [11]. In the present study, we measured both serum lignocaine concentrations and cumulative lignocaine doses. There were no significant differences between the groups in the seizure threshold in our study, regardless of the criteria used to define seizures. In addition, we found no correlation between the cumulative dose of lignocaine and the measured serum lignocaine concentrations, suggesting that these measurements of lignocaine seizure thresholds cannot be used interchangeably.

The fact that no difference was noted in the lignocaine seizure threshold after pretreatment with atracurium *v.* vecuronium and pancuronium may be attributable to a number of factors. First, the production of laudanosine by the doses of atracurium used may have been insufficient to produce a change in seizure threshold [6]. Second, histamine release following atracurium may have been insufficient to alter cerebral function meaningfully, or the cerebral effects of histamine may have been negated by controlling Pa_{CO_2}. Third, the reported cerebral effects of the neuromuscular blockers studied [5, 6] may affect the brain by mechanisms which are independent of the mechanisms by which lignocaine alters cerebral function.

In summary, we could find no difference in lignocaine seizure thresholds among groups of halothane-anaesthetized cats pretreated with atracurium, vecuronium or pancuronium. Assuming our data in cats are transferable to man, we conclude that intubating doses of the three drugs studied can be interchangeably administered in patients also receiving lignocaine without increasing the relative risk of lignocaine-induced convulsions.

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EFFECTS OF THE PATTERN OF VENTILATION AND OF AN INCREASE IN CARDIAC OUTPUT ON THE DISTRIBUTION OF BLOOD FLOW TO A HYPOXIC LUNG LOBE

D. CANNON, E. J. KALSO AND M. K. SYKES

SUMMARY

Electromagnetic flow probes were used to measure the fraction of the pulmonary blood flow perfusing the left lower lobe ($\dot{Q}l/\dot{Q}t$) in 16 anaesthetized, open-chest dogs in order to study the effects of right lung airway pressure on the distribution of blood flow to a hypoxic lung lobe. Ventilation of the lobe with 7% oxygen in nitrogen resulted in a 37% reduction in $\dot{Q}l/\dot{Q}t$ at the beginning and end of the main procedure, thus confirming that the hypoxic pulmonary vasoconstrictor response was unchanged throughout the study. The effects of varying mean airway pressure to the right lung by changing inspiratory:expiratory time ratio and by the addition of a positive end-expiratory pressure were studied when the left lower lobe was insufflated with oxygen or 7% oxygen in nitrogen, or was collapsed. Insufflation of the lobe with 7% oxygen in nitrogen and collapse reduced $\dot{Q}l/\dot{Q}t$ by 61% and 66%, respectively. However, changing mean airway pressure in the right lung produced no significant changes in $\dot{Q}l/\dot{Q}t$ in any of the different lobar conditions or when collapse was produced after fluid loading. Fluid loading during collapse increased cardiac output and pulmonary vascular pressures and increased $\dot{Q}l/\dot{Q}t$ to a value which was not significantly different from lobar ventilation with 7% oxygen in nitrogen. It is concluded that moderate increases in mean airway pressure do not increase $\dot{Q}l/\dot{Q}t$ when this has been reduced by exposure of the lobe to mixed venous blood-gas tensions.

Severe arterial hypoxaemia resulting from acute lung disease is frequently treated with positive end-expiratory pressure (PEEP) or an increase in inspiratory:expiratory (I:E) time ratio, the latter being produced either by a reduction in inspiratory flow rate or by the addition of an inspiratory pressure plateau. The reduction in shunt associated with PEEP or an increase in I:E ratio is probably a result of the recruitment of previously collapsed alveoli secondary to an increase in end-expiratory lung volume [1]. However, the improved oxygenation appears to be related most closely to the increase in mean airway pressure [2], and there is evidence that the addition of an inspiratory pressure plateau can decrease shunt even though end-expiratory volume is little changed [3].

In some patients normal values of PEEP produce little improvement in oxygenation, whilst higher values may increase alveolar deadspace and intrapulmonary shunt [4–6]. The increase in shunt with PEEP has been noted most frequently in patients with predominantly unilateral lung disease and there is evidence that, in these circumstances, PEEP may redistribute blood flow from the well-ventilated to the diseased area of lung [7–9]. The application of PEEP may also decrease cardiac output and mixed venous Po_2. If shunt is unchanged, this will result in a reduction in arterial Po_2. The reduction in cardiac output may be minimized by fluid loading or the use of

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inotropic drugs, but these interventions may in themselves increase shunt in patients with acute lung disease [6, 10–12].

There is now strong evidence that the reduction in blood flow in a collapsed area of lung is predominantly caused by hypoxic pulmonary vasoconstriction (HPV) augmented by the increase in $P\text{CO}_2$ which results from the equilibration of the lobe with mixed venous blood [13]. In order to determine whether this mechanism remained effective when increased airway pressures were applied to the rest of the lung, we have used electromagnetic flow probes to measure the distribution of blood flow between a ventilated (right) lung and a hypoxic left lower lobe in anaesthetized open-chest dogs. This preparation enabled us to study the effects of different patterns of ventilation applied to the right lung during three different conditions of the lobe and to assess the effects of increased cardiac output produced by fluid loading.

MATERIALS AND METHODS

Anaesthesia was induced in 17 dogs of either sex and mixed breed (weight 19.7 ± 5.0 kg) using sodium thiopentone 20–25 mg kg^{-1} i.v., following premedication with morphine sulphate 1.5–2.0 mg kg^{-1}. Anaesthesia was maintained with 1.5 % halothane for the duration of surgery and, thereafter, with 0.5 % halothane in oxygen to the right lung and an i.v. infusion of Hypnorm (Janssen: fentanyl citrate 0.315 mg ml^{-1}, fluanisone 10 mg ml^{-1}) at a rate of 0.06 ml kg^{-1}. After intubation of the trachea with a 9.0-mm i.d. cuffed tracheal tube, the lungs were ventilated initially with a Cape–Waine ventilator. Tidal volume was adjusted to give an end-tidal carbon dioxide concentration of 4.0–4.5 % at a frequency of 10 b.p.m. $F\text{I}_{\text{O}_2}$ was maintained at 1.0 and a positive end-expiratory pressure of 1.0–2.0 mm Hg was applied throughout the surgical preparation. Body temperature was maintained at 38.0 ± 0.5 °C, the ECG and arterial pressure were monitored continuously and base excess was maintained at 1.2 ± 0.5 mmol litre^{-1} by the administration of 4.2 % sodium bicarbonate. A continuous infusion of Haemaccel (Hoechst U.K. Ltd) was given to maintain the haematocrit between 30 and 35 %.

Tracheotomy was performed and a double-lumen PVC endobronchial tube was inserted (35 French gauge, International Catheter Corp.), the bronchial tube being passed into the left main bronchus. The position was confirmed by auscultation and measurement of airway pressures when equal tidal volumes were applied to each lung. The complete isolation of each lung was verified by connecting the left limb of the tube to an underwater seal while the right lung was pressurized to +30 cm H_2O. The left lung was then collapsed whilst the remainder of the surgery was performed.

A left lateral thoracotomy was performed between the 5th and 6th ribs and the collapsed upper and cardiac lobes were removed to facilitate further surgery. The main trunk of the pulmonary artery and the artery to the left lower lobe were freed from the surrounding connective tissue and Gould–Statham SP7156 electromagnetic flow probes, fed by synchronized excitation currents from SP2204 flowmeters, were placed round the arteries for blood flow measurements. Catheters for pressure measurement were placed in the pulmonary arterial trunk via the stump of the left upper lobar artery and in the left atrium via the atrial appendage.

The left lower lobe was then reinflated and the right lung and lobe ventilated independently by a double "bellows-in-box" system which allowed control of the tidal volume and gas composition delivered to each lung (fig. 1). The bellows were compressed by a modified Nuffield anaesthetic ventilator 200 (Penlon Ltd, Abingdon) at a rate of 10 b.p.m., the pattern of ventilation being altered by the inspiratory and expiratory time controls and by the adjustment of magnetic PEEP valves (BE142 Instrumentation Industries Inc.). On completion of the surgery, the lung and lobe were ventilated with an I:E ratio of 1:2 and PEEP of 2.8 ± 1.2 mm Hg, and the tidal volumes adjusted to produce equal end-tidal carbon dioxide concentrations within the normal range. The preparation was allowed to stabilize for 1–2 h, during which the lobe was subjected to several periods of ventilation with 7 % oxygen in nitrogen to ensure that a maximal hypoxic response had been obtained.

A 16-stage experimental programme was used with a 15–20 min stabilization period at each stage. The right lung was ventilated with $F\text{I}_{\text{O}_2}$ 1.0 throughout the experiment, the period of study lasting 6–7 h. During stages 1 and 2, the left lower lobe was ventilated with oxygen and then with 7 % oxygen in nitrogen to establish the control response to hypoxia. This test was repeated

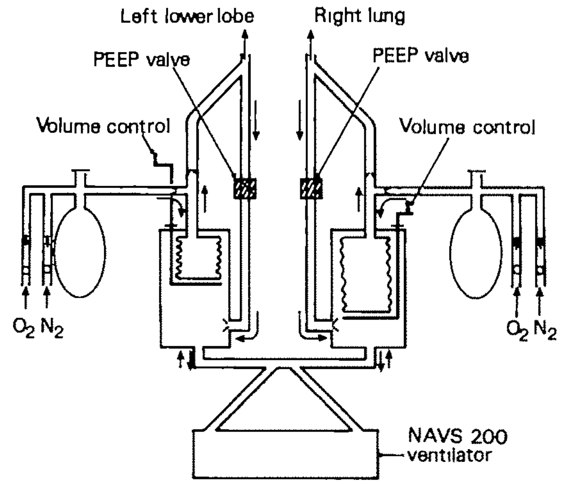

FIG. 1. Second stage "bellows-in-the-box" system used to ventilate the right lung and left lower lobe independently with varying oxygen and nitrogen mixtures. During insufflation of the lobe a clamp was placed across the tube connecting the driving ventilator to the lobe "bellows-in-box", whilst the expiratory tube was disconnected from the box so that the PEEP valve could be used to control mean airway pressure.

towards the end of the experiment (stages 12 and 13). Three patterns of ventilation were applied to the right lung during each lobe condition (fig. 2). These were:

(1) an I:E ratio of 1:2 with minimal PEEP (1:2);

(2) an I:E ratio of 2:1 with minimal PEEP (2:1);

(3) an I:E ratio of 1:2 with PEEP adjusted to achieve the same mean airway pressure ($P_{\overline{aw}}$) as was recorded with the long inspiratory period (1:2+P).

The three patterns of right lung ventilation were repeated whilst the left lower lobe was exposed to four different conditions. The first two were insufflation of the left lower lobe with either 100% oxygen or 7% oxygen in nitrogen with lobar PEEP adjusted to give the same $P_{\overline{aw}}$ as during ventilation with 100% oxygen, the insufflation being started after 10 min ventilation of the lobe with the insufflation gas mixture. The third condition was left lower lobe collapse with the lobe connected to an underwater seal, whilst the fourth condition was collapse with the cardiac output increased by the rapid infusion of 1.0–1.5 litre of Haemaccel. The order of the first three lobar states was randomized (stages 3–11), but the fluid loading was always carried out at the end of the experiment (stages 14–16).

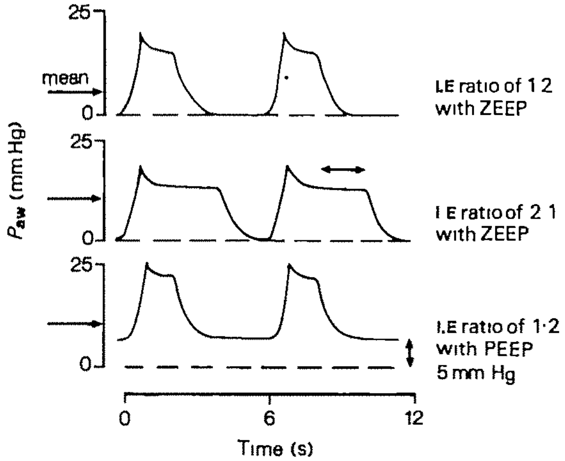

FIG. 2. Patterns of ventilation applied to the right lung. The mean airway pressures with the ratios 2:1 and 1:2+PEEP were the same. ZEEP = Zero end-expiratory pressure.

Each of the recorded variables was analysed using a two-way analysis of variance. This allowed the independent assessment of the effects of changes in the pattern of right lung ventilation, and of changes in left lower lobe conditions. Comparison of individual stages was by Student's *t* test at the 5% level. Related comparisons were grouped and the required level of significance adjusted for the number of comparisons using Sidak's inequality [14].

The above programme and analyses were carried out in two groups of dogs. The first group (numbers 1–11) were given soluble aspirin 50 mg kg^{-1} i.v. at the end of surgery to optimize the HPV response [15] and the dogs were turned to the prone position for the duration of the experiment. The second group (numbers 12–16) did not receive aspirin and remained in the supine position. A comparison of the two groups for all variables indicated no significant differences, so the data for both groups were subsequently pooled and analysed as a single group.

RESULTS

The results are shown in tables I and II. With the exception of mixed venous Po_2 ($P\bar{v}_{O_2}$), there were no significant differences in any variable between the first and second control stages (1 and 12). Lobar ventilation with 7% oxygen in nitrogen (stage 2) produced a 37% reduction in the ratio of left lower lobar blood flow to pulmonary arterial blood flow ($\dot{Q}l/\dot{Q}t$) (fig. 3) and resulted in a

TABLE I. *Changes in total* (Q̇t) *and lobar* (Q̇l) *pulmonary blood flow, and vascular and airway pressures throughout the experiment (means ± SEM). Left lower lobe (LLL) conditions: V = ventilation; I = insufflation. Right lung conditions: inspiratory : expiratory time ratio ± PEEP (P); +FL = after fluid loading.* $P_{\overline{PA}}$ *and* $P_{\overline{LA}}$ = *Mean pulmonary artery and left atrial pressures; SAP = systolic arterial pressure,* $P_{\overline{law}}$, $P_{\overline{raw}}$, *peak* P_{raw} *and R PEEP = left and right mean, peak and end-expiratory airway pressures, respectively. Statistically significant differences between stages* ($P < 0.05$) *indicated by numbers in parentheses*

Stage	LLL condition	R. lung condition	*n*	Q̇t (litre min⁻¹)	Q̇l/Q̇t (%)	$P_{\overline{PA}}$ (mm Hg)	$P_{\overline{LA}}$ (mm Hg)	SAP (mm Hg)	$P_{\overline{raw}}$ (mm Hg)	Peak P_{raw} (mm Hg)	R. PEEP (mm Hg)	$P_{\overline{law}}$ (mm Hg)
1	100 % O_2 V	1 : 2	16	1.50 ±0.11	31.7 ±1.7	17.3 ±0.8	8.5 ±0.8	133.7 ±4.0	7.1 ±0.3	18.0 ±0.6	2.8 ±0.3	7.1 ±0.2
2	7 % O_2 V	1 : 2	16	1.49 ±0.11	20.1 ±1.7 (1)	18.7 ±0.8	9.0 ±0.8	131.4 ±4.0	7.3 ±0.3	18.4 ±0.6	2.8 ±0.3	7.4 ±0.2
3	100 % O_2 I	1 : 2	16	1.33 ±0.10	28.4 ±1.7	17.1 ±0.8	9.5 ±0.7	123.4 ±3.9	7.2 ±0.3	17.2 ±0.6	2.6 ±0.2	6.9 ±0.2
4	100 % O_2 I	2 : 1	16	1.39 ±0.11	30.0 ±1.7	17.8 ±0.8	7.5 ±0.8	120.7 ±4.0	10.5 ±0.3 (1, 2, 3)	16.5 ±0.6	3.3 ±0.3	6.8 ±0.2
5	100 % O_2 I	1 : 2P	16	1.34 ±0.11	32.0 ±1.7	17.6 ±0.8	7.1 ±0.8	119.8 ±4.0	10.4 ±0.3 (1, 2, 3)	21.0 ±0.6 (3, 4)	5.8 ±0.2 (3, 4)	6.7 ±0.2
6	7 % O_2 I	1 : 2	16	1.47 ±0.11	12.4 ±1.7 (5, 13)	17.7 ±0.8	7.8 ±0.8	117.6 ±4.0	7.0 ±0.3	17.9 ±0.6	2.5 ±0.2	6.6 ±0.2
7	7 % O_2 I	2 : 1	15	1.38 ±0.11	10.8 ±1.8 (2–5, 13)	18.9 ±0.8	8.3 ±0.8	112.7 ±4.2	9.6 ±0.3 (6)	16.0 ±0.6	2.7 ±0.3	6.5 ±0.2
8	7 % O_2 I	1 : 2P	15	1.40 ±0.11	11.7 ±1.8 (2–5, 13)	19.7 ±0.8	7.5 ±0.8	115.4 ±4.2	10.4 ±0.3 (6)	27.0 ±0.6 (6, 7)	6.7 ±0.3 (6, 7)	6.9 ±0.2
9	Collapse	1 : 2	15	1.34 ±0.11	10.7 ±1.8 (2–5, 13)	17.8 ±0.8	7.9 ±0.8	106.0 ±4.2 (1–8)	6.4 ±0.3	17.6 ±0.7	2.2 ±0.3	
10	Collapse	2 : 1	15	1.30 ±0.11	12.8 ±1.8 (2–5, 13)	18.5 ±0.8	7.8 ±0.8	105.4 ±4.2 (1–8)	9.7 ±0.3 (9)	15.9 ±0.7	2.5 ±0.3	
11	Collapse	1 : 2P	15	1.27 ±0.11	12.2 ±1.8 (2–5, 13)	19.2 ±0.8	7.8 ±0.8	107.0 ±4.2 (1–8)	9.9 ±0.3 (9)	20.8 ±0.7 (9, 10)	5.8 ±0.3 (9, 10)	
12	100 % O_2 V	1 : 2	13	1.30 ±0.12	31.4 ±1.9	17.6 ±1.0	8.0 ±0.8	114.3 ±4.5 (1, 2, 9–11)	6.8 ±0.3	17.6 ±0.7	1.8 ±0.3	6.9 ±0.2
13	7 % O_2 V	1 : 2	13	1.38 ±0.12	19.9 ±1.9 (12)	16.9 ±0.9	8.0 ±0.8	112.8 ±4.5 (1, 2, 9–11)	6.9 ±0.3	18.2 ±0.7	2.0 ±0.3	7.7 ±0.2
14	Collapse	1 : 2+FL	8	3.54 ±0.16 (1–13)	19.6 ±2.5 (3–12)	32.5 ±1.2 (1–13)	20.8 ±1.1 (1–13)	117.6 ±5.8 (1, 2)	6.9 ±0.4	21.2 ±0.9	1.8 ±0.4	
15	Collapse	2 : 1+FL	7	3.84 ±0.17 (1–13)	21.0 ±2.6 (3–12)	35.2 ±1.2 (1–13)	24.0 ±1.2 (1–13)	136.6 ±6.2 (6–13)	9.7 ±0.4 (14)	18.5 ±0.9	1.9 ±0.4	
16	Collapse	1 : 2P+FL	7	3.65 ±0.17 (1–13)	22.4 ±2.6 (3–12)	33.3 ±1.2 (1–13)	23.4 ±1.2 (1–13)	135.2 ±6.2 (6–13)	9.6 ±0.4 (14)	22.9 ±0.9 (14, 15)	3.7 ±0.4 (14, 15)	

TABLE II. *Changes in arterial and mixed venous blood-gas tensions, arterial pH, left and right end-tidal carbon dioxide concentration* (lE'_{CO_2}, rE'_{CO_2}) *at various stages of the experiment. Statistically significant differences between stages* ($P < 0.05$) *indicated by numbers in parentheses. Conditions as in table I*

Stage	LLL condition	R. lung condition	n	Pa_{O_2} (kPa)	Pa_{CO_2} (kPa)	pH	$P\bar{v}_{O_2}$ (kPa)	$P\bar{v}_{CO_2}$ (kPa)	lE'_{CO_2} (%)	rE'_{CO_2} (%)
1	100 % O_2 V	1 : 2	16	67.1 ±3.2	5.1 ±0.2	7.44 ±0.01	7.1 ±0.2	6.0 ±0.1	4.5 ±0.1	4.5 ±0.1
2	7 % O_2 V	1 : 2	16	46.0 ±3.2 (1)	4.9 ±0.2	7.43 ±0.01	6.7 ±0.2	6.2 ±0.1	4.0 ±0.2	4.6 ±0.1
3	100 % O_2 I	1 : 2	16	64.7 ±3.1	5.3 ±0.1	7.39 ±0.01	7.1 ±0.2	6.6 ±0.1		4.4 ±0.2
4	100 % O_2 I	2 : 1	16	63.5 ±3.5	5.9 ±0.2 (3)	7.35 ±0.01	7.1 ±0.2	7.0 ±0.1		5.3 ±0.3
5	100 % O_2 I	1 : 2P	16	67.0 ±3.2	5.5 ±0.2	7.38 ±0.01	6.9 ±0.2	6.8 ±0.1		5.1 ±0.3
6	7 % O_2 I	1 : 2	16	53.1 ±3.3 (3–5)	5.3 ±0.2	7.39 ±0.01	6.6 ±0.2 (1–5)	6.6 ±0.1		4.8 ±0.2
7	7 % O_2 I	2 : 1	15	53.1 ±3.4 (3–5)	5.5 ±0.2	7.38 ±0.01	6.6 ±0.2 (1–5)	6.7 ±0.2		5.5 ±0.4
8	7 % O_2 I	1 : 2P	15	52.3 ±3.4 (3–5)	5.3 ±0.2	7.39 ±0.01	6.4 ±0.2 (1–5)	6.6 ±0.2		5.3 ±0.4
9	Collapse	1 : 2	15	49.5 ±3.5 (3–5)	5.5 ±0.2	7.38 ±0.01	6.5 ±0.2 (1–5)	6.8 ±0.2		4.9 ±0.3
10	Collapse	2 : 1	15	48.3 ±3.5 (3–5)	5.8 ±0.2	7.35 ±0.01	6.4 ±0.2 (1–5)	7.0 ±0.2		5.5 ±0.3
11	Collapse	1 : 2P	15	52.1 ±3.5 (3–5)	5.3 ±0.1	7.38 ±0.01	6.2 ±0.2 (1–5)	6.8 ±0.2		5.4 ±0.4
12	100 % O_2 V	1 : 2	13	68.1 ±3.8 (6–11)	4.8 ±0.2	7.42 ±0.01	6.3 ±0.2 (1–5)	6.1 ±0.2	4.3 ±0.2	4.5 ±0.2
13	7% O_2 V	1 : 2	13	44.5 ±3.8 (12)	4.7 ±0.2	7.41 ±0.01	5.7 ±0.2 (1–5)	5.8 ±0.2	3.6 ±0.2	4.5 ±0.2
14	Collapse	1 : 2+FL	8	48.4 ±5.0 (3–5)	5.7 ±0.2	7.27 ±0.02 (1–13)	8.3 ±0.3 (1–13)	6.4 ±0.2		5.0 ±0.2
15	Collapse	2 : 1+FL	7	48.0 ±4.7 (3–5)	5.7 ±0.2	7.34 ±0.02 (12, 13)	7.4 ±0.3 (1–13)	6.7 ±0.2		5.7 ±0.2
16	Collapse	1 : 2P+FL	7	49.6 ±4.7 (3–5)	5.8 ±0.2	7.34 ±0.02 (12, 13)	7.4 ±0.3 (1–13)	6.6 ±0.2		5.4 ±0.2

reduction in arterial Po_2 from 67.7 kPa to 46.0 kPa and a decrease in lobar end-tidal carbon dioxide from 4.5% to 4.0%. The response to ventilation hypoxia at stage 13 was not significantly different from that at stage 2. The lobar $P_{\overline{aw}}$ was similar during ventilation with 100% oxygen (stage 1) and insufflation of the lobe with 100% oxygen (stages 3, 4 and 5), and $\dot{Q}l/\dot{Q}t$ was similar in the two conditions. There was a significant reduction in $\dot{Q}l/\dot{Q}t$ during insufflation of the lobe with 7% oxygen (stages 6, 7 and 8), and during collapse (stages 9, 10 and 11) (fig. 4), but there was no significant difference in $\dot{Q}l/\dot{Q}t$ between these two states of the lobe.

The change in the pattern of right-lung ventilation from an I:E ratio of 1:2 (stages 3, 6 and 9) to one of 2:1 (stages 4, 7 and 10) resulted in significant increases in right mean airway pressure

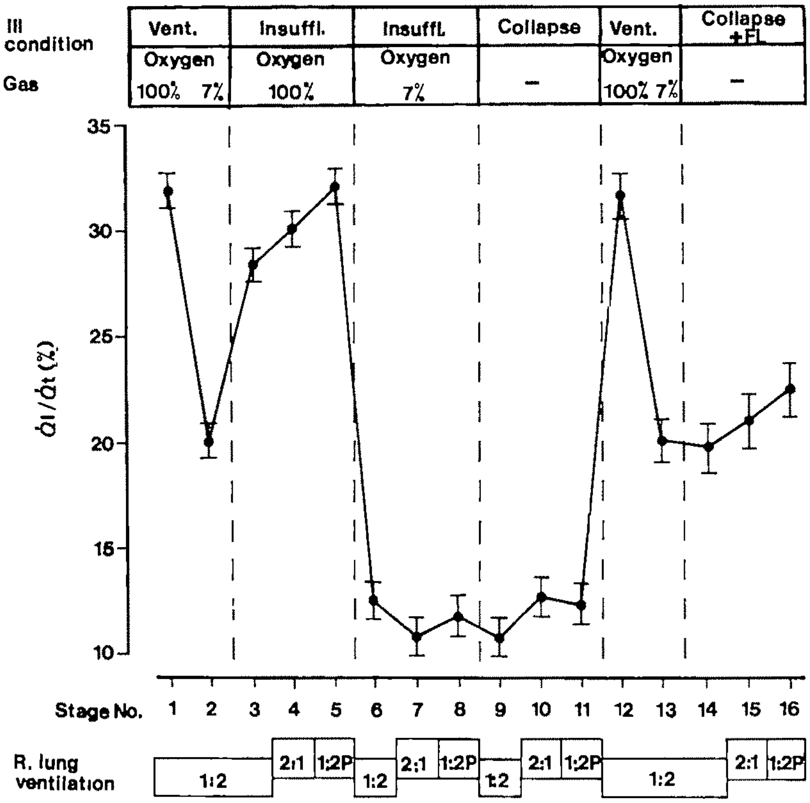

FIG. 3. Proportion of the cardiac output perfusing the left lower lobe ($\dot{Q}l/\dot{Q}t$) (means ± SEM). The lobar conditions (response to ventilation with 7% oxygen in nitrogen, insufflation with 100% oxygen or 7% oxygen in nitrogen and collapse) are indicated at the top of the graph, whilst the patterns of right lung ventilation are demarcated at the bottom.

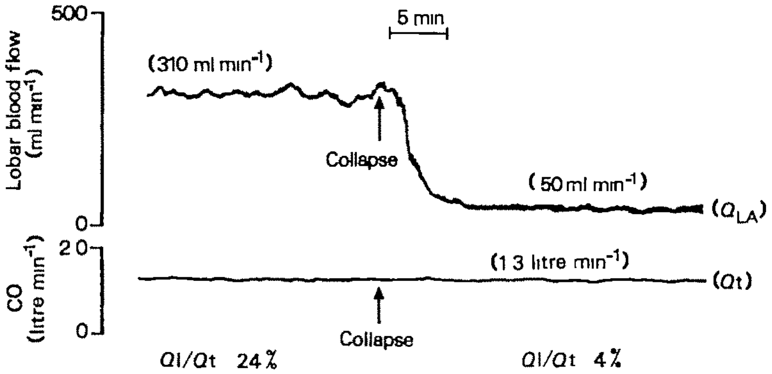

FIG. 4. Reduction in lobar blood flow following collapse in one dog with a good HPV response. CO = Cardiac output ($\dot{Q}t$); $\dot{Q}_{LA}$ = flow perfusing left lower lobe artery.

($P_{\overline{raw}}$) of approximately 3 mm Hg without any significant changes in right peak airway pressure (peak P_{raw}). There were no significant differences between $P_{\overline{raw}}$ with the 2:1 ratio and the 1:2 ratio plus PEEP (stages 5, 8 and 11), although there were significant increases in peak P_{raw} with the latter pattern of ventilation. However, these changes in ventilatory pattern had no significant effects on $\dot{Q}l/\dot{Q}t$, $P_{\overline{PA}}$, $P_{\overline{LA}}$ or arterial and mixed venous Po_2 (Pa_{O_2}, $P\bar{v}_{O_2}$) within each of the states of the left lower lobe.

Infusion of Haemaccel resulted in a significant increase in $\dot{Q}t$, $P_{\overline{PA}}$, $P_{\overline{LA}}$, Pa_{O_2}, and $P\bar{v}_{O_2}$, whilst $\dot{Q}l/\dot{Q}t$ was increased to a value which was not significantly different from ventilation of the lobe with 7% oxygen in nitrogen (stages 2 and 13).

DISCUSSION

These investigations showed that collapse, or insufflation of the lobe with 7% oxygen in nitrogen, produced a greater reduction in $\dot{Q}l/\dot{Q}t$ than did ventilation with 7% oxygen in nitrogen, although mean airway pressures in the lobe were similar during insufflation and ventilation. However, there were no significant differences between ventilation of the lobe with oxygen and insufflation with oxygen. An increase in $P_{\overline{aw}}$ in the right lung produced by changing the I:E ratio to 2:1 or the addition of PEEP to the 1:2 ratio did not affect $\dot{Q}l/\dot{Q}t$ in any condition of the left lower lobe. During lobar collapse, increasing the cardiac output by fluid loading resulted in a redistribution of blood flow towards the collapsed left lower lobe so that values of $\dot{Q}l/\dot{Q}t$ were not significantly different from those found during lobar ventilation with 7% oxygen in nitrogen.

Results obtained in the open-chest preparation in anaesthetized dogs must be interpreted with caution, for the normal vertical gradient of subatmospheric pleural pressure is abolished [16]. This may result in changes in functional residual capacity and in the distribution of ventilation and blood flow. It may also reduce venous return and cardiac output—effects which are compounded by the deeper level of anaesthesia required in the open-chest preparation. Further abnormalities are introduced by the reduction in pulmonary vascular volume following the removal of the left upper and cardiac lobes and the probable denervation of the pulmonary vascular bed during the placement of the electromagnetic flow probes. However, flow distribution in the control periods was similar to the distribution of blood flow in the conscious animal [17] and the response to hypoxia was similar to that observed in other preparations [18, 19].

Aspirin was administered to the first 11 dogs in order to minimize the delay in establishing a maximal response to alveolar hypoxia [15] and these dogs were turned to the prone position after surgery to retain the normal zone relationships between the lungs and heart. Since preliminary analysis of these data showed no changes in $\dot{Q}l/\dot{Q}t$ in response to changes in $P_{\overline{aw}}$ in the right lung, the next six procedures were conducted in the supine position without aspirin. There were no significant differences between the two groups and it was concluded, therefore, that neither of these factors had affected the results.

Insufflation of the lobe with 7% oxygen in nitrogen produced a greater reduction in $\dot{Q}l/\dot{Q}t$ (61%) than did ventilation with the same gas mixture (37%). Since $P_{\overline{aw}}$ was similar in the two conditions, this suggests that the difference in $\dot{Q}l/\dot{Q}t$ must have resulted from differences in the alveolar gas tensions. During insufflation, the alveolar Po_2 and Pco_2 should have equilibrated with mixed venous Po_2 and Pco_2 [20]. Ventilation with 7% oxygen in nitrogen has been shown to produce pulmonary vein Po_2 values close to mixed venous ones [13], although Pco_2 values are lower than mixed venous, the alveolar Pco_2 depending on the ratio of ventilation to perfusion in the lobe. Thus, the observation that $\dot{Q}l/\dot{Q}t$ was lower during insufflation hypoxia (stages 6, 7 and 8) than during ventilation hypoxia with a lobar end-tidal carbon dioxide concentration of 4.0–3.6% (stages 2 or 13), confirms previous observations which suggest that HPV is augmented by an increase in Pco_2 [21]. However, carbon dioxide appears to have little effect on the hyperoxic vascular bed, for there was no difference in $\dot{Q}l/\dot{Q}t$ between stage 1 (ventilation with oxygen) and stages 3–5 (insufflation with oxygen). A further indication of the importance of alveolar gas tensions in the control of flow through the hypoxic lobe is the observation that insufflation of the lobe with 7% oxygen in nitrogen and collapse produced similar reductions in $\dot{Q}l/\dot{Q}t$ (61% and 66%, respectively) even though lung volume and transpulmonary pressure were markedly different in the two conditions. This confirms other observations which suggest that mechanical factors contribute little to the reduction in blood flow in a collapsed area of lung [13, 22–24].

In the present studies an increase in $P_{\overline{aw}}$ produced by the addition of PEEP or the use of a 2:1 ratio had no significant effect on $\dot{Q}l/\dot{Q}t$ in any state of the left lower lobe. Similar results were obtained by Enjeti and colleagues [25], who found that perfusion of a collapsed sub-lobar segment in a closed-chest preparation was not affected by the application of PEEP to adjacent normoxic ventilated segments. However, other authors have found that flow diversion does occur in response to changes in airway pressure in the ventilated lung. Takaro [26] showed a marked diversion of flow into a hypoxic–hypercarbic lung when standing pressures of 15 or 25 cm H_2O were applied to the opposite lung for periods of 20 s in the closed-chest dog. In open-chest dogs, Benumof and co-workers [27] found that flow to a collapsed left lower lobe was increased when right lung PEEP was increased from 2 to 10 cm H_2O, whilst Sanchez de Leon and associates [28] found a similar shift into a collapsed left lower lobe in response to the application of 5–15 cm H_2O PEEP.

There are several possible explanations for the lack of change of $\dot{Q}l/\dot{Q}t$ in response to changes in $P_{\overline{aw}}$ in the present experiments. First, blood flow through zone 2 of the ventilated lung is governed by the relationship between alveolar and pulmonary artery pressure. In our experiments, blood volume was carefully maintained during surgery and $P_{\overline{PA}}$ was relatively high during the experimental period, whilst the changes in $P_{\overline{aw}}$ were smaller than those imposed by Benumof and colleagues [27] and Sanchez de Leon and co-workers [28]. However, in seven of the dogs we applied sequential increases in $P_{\overline{aw}}$ up to 15 mm Hg and found diversion of blood flow to be minimal (fig. 5). Whittenberger and colleagues [29] showed that pulmonary vascular resistance in

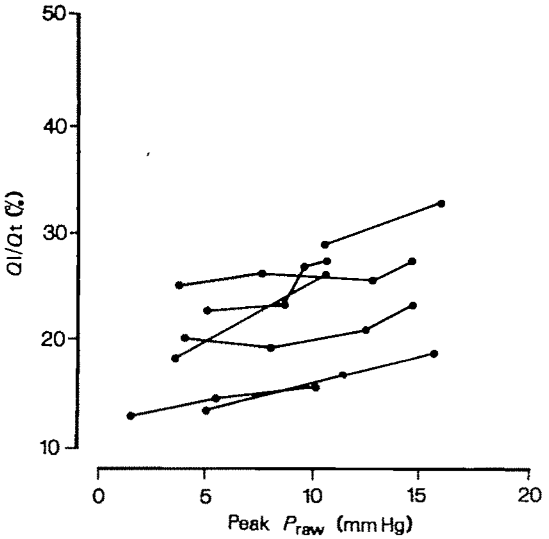

FIG. 5. Changes in $\dot{Q}l/\dot{Q}t$ in seven dogs in which sequential increases in static airway pressure were applied to the right lung.

isolated perfused lungs was little changed by increases in $P_{\overline{aw}}$ up to 15 mm Hg, but that resistance was increased at greater mean airway pressures. However, $P_{\overline{PA}}$ was also high in these experiments.

A second possibility is that the initial lung volumes may have been different. Benumof and colleagues [27] found that the diversion of flow in response to PEEP was much greater when the chest was open than when it was closed and suggested that differences in FRC may have contributed to the different results obtained. It is known that pulmonary vascular resistance is minimal at FRC and increases when lung volume is decreased or increased [30]. If the initial volume of the right lung was below the normal FRC, the addition of PEEP would have tended to decrease PVR in that lung rather than increase it, and this would have minimized any diversion of flow away from that lung.

A third explanation for the disparity in results is that the HPV response may have been optimal in our experiments. Great care was taken to ensure that the lobe was not handled during surgery to avoid the generation of vasodilator substances such as prostacyclin, and the lung was subjected to repeated hypoxic stimuli before the definitive study was commenced to ensure that the response was maximal. The opposing effects of an increase in airway pressure, and HPV, on the distribution of blood flow are well illustrated by the experiments of Mink and associates [8]. These authors found that the application of 12 cm H_2O PEEP increased $\dot{Q}l/\dot{Q}t$ from 24% to 37% in experimental left lower lobe pneumonia. However, they noted that there was little diversion of flow away from lobes with high bacterial counts and attributed the diversion of flow in response to PEEP to the relatively weak HPV response during the acute phase of the disease.

The increase in cardiac output before the final period of lobar collapse increased $\dot{Q}l/\dot{Q}t$ to values not significantly different from those found during lobar ventilation with 7% oxygen in nitrogen. Benumof and Wahrenbrock [19] demonstrated a reduction in the magnitude of flow diversion in response to hypoxia when pulmonary vascular pressures were increased by inflation of a left atrial balloon or by fluid loading and concluded that the increase in intravascular pressure opposed the increased vascular tone resulting from HPV so that lobar flow increased. However, in the present study there was also a significant increase in $P\bar{v}_{O_2}$ which would have reduced the stimulus for HPV in the lobe, and so increased $\dot{Q}l/\dot{Q}t$ [31–33].

In view of the lack of change in $\dot{Q}l/\dot{Q}t$ in response to changes in right lung $P_{\overline{aw}}$, it is not surprising that the changes in $P_{\overline{aw}}$, also had no effect when $P_{\overline{PA}}$ was increased by fluid loading.

It is concluded that, in the open-chest preparation, changes in $P_{\overline{aw}}$ in ventilated areas of lung probably cause a shift of blood flow into poorly ventilated lung only when the increase in $P_{\overline{aw}}$ is greater than 5–10 mm Hg. The magnitude of flow diversion is probably dependent on the relationship between the $P_{\overline{aw}}$ and the $P_{\overline{PA}}$, and the strength of the HPV response. However, when the chest is closed, the shift of blood flow in response to an increase in $P_{\overline{aw}}$ may be different. Furthermore, under these circumstances, the application of PEEP may decrease cardiac output and $P\bar{v}_{O_2}$. If PEEP does not reduce shunt, the reduced saturation of the blood passing through the shunt may result in a reduction in arterial P_{O_2} [34].

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PULMONARY TOXICITY AFTER TREATMENT WITH BLEOMYCIN ALONE OR IN COMBINATION WITH HYPEROXIA

Studies in the Rat

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SUMMARY

Female Wistar rats (n = 11) received bleomycin 10 mg kg^{-1} i.p. three times weekly for 6 weeks. Four weeks later part of the group (n = 7) were exposed to 50% oxygen in air for 4 h; the others served as unexposed controls. A further control group (n = 5) received physiological saline i.p. and was not exposed to oxygen. One week after the hyperoxia treatment all animals were sacrificed and the lungs prepared for histological and biochemical determinations. Although the average body weight of the bleomycin-treated rats decreased significantly compared with the saline-treated controls, no significant alterations in lung histology were found in regard to the occurrence of oedema, fibrosis, and type II pneumocytes. Intra-alveolar macrophages were significantly increased. Subsequent hyperoxia did not lead to a more pronounced effect, except for macrophage accumulation. The activities of superoxide dismutase and glutathione peroxidase were not changed either after administration of bleomycin alone or after combination with hyperoxia. It is concluded that bleomycin i.p. in doses comparable to those encountered clinically, administered alone or combined with hyperoxia, does not result in pulmonary damage in female Wistar rats.

Concern has been expressed in regard to the possible toxic effects of hyperoxia on drug-sensitized lung tissue [1]. An increase in the toxicity of high concentrations of oxygen has been demonstrated in rodents after the administration of a variety of chemicals, including, for example, butylated hydroxytoluene [2]. For a number of compounds, such as paraquat and diquat, this has also been demonstrated in man [3]. In rodents, a similar degree of oxygen toxicity has been described in association with the combination of hyperoxia and the antineoplastic drug, bleomycin [4–8]. In man, treatment with bleomycin followed by high concentrations of oxygen is suspected of being a cause of pulmonary toxicity, as has been observed in bleomycin-treated patients after surgery [9]. This suspicion has led the anaesthetist to omit the use of hyperoxia during anaesthesia in bleomycin-treated patients, although doubt concerning the possible additive role of oxygen in bleomycin-induced pulmonary toxicity has been expressed [10, 11]. Since there is evidence that bleomycin exhibits its anti-tumour effect by generating oxygen radicals that disintegrate cellular DNA [12], the combination of bleomycin and high oxygen tensions may lead to superimposed toxicity.

In this respect, tissues with low bleomycin hydrolase activity, such as lung and skin, might be

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most susceptible [13]. Agents which produce oxidative damage of the lung may stimulate lung defense mechanisms, which will limit injury as a result of a second insult by the same or a different agent. In this regard superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) may be important [14]. Apart from an augmentation of these enzymes after the first oxidative challenge, it is also possible that the activity decreases because of destruction of the enzymes and the enzyme synthetic machinery. If activated oxygen species are playing an important role in bleomycin-induced pulmonary toxicity with or without hyperoxia, alterations in the activities of SOD and GSH-Px may be expected.

The purpose of this study was to investigate pulmonary toxicity in rats after treatment with doses of bleomycin approaching those encountered clinically in the presence or absence of additional hyperoxia. Lung morphology was studied and the possible induction of protecting enzymes (SOD and GSH-Px) was assayed.

MATERIALS AND METHODS

Design of investigation

Female Wistar rats, bred under specific pathogen-free conditions (until weaning) were obtained from the Central Institute for the Breeding of Laboratory Animals (Zeist, The Netherlands). At the start of the investigation the animals were 11 weeks old and weighed 170 ± 10 g. They were housed in a laminar flow cabinet, at most three in a cage. They received sterilized rat chow (RMH-B Hope Farms, Woerden, The Netherlands) and acidified water *ad libitum*. After an adaptive phase of 5 weeks, i.p. injections of bleomycin sulphate 10 mg kg^{-1} (Lundbeck, Copenhagen, Denmark) dissolved in 0.5 ml of sterile physiological saline, were performed in 11 rats three times weekly for a period of 6 weeks. Immediately before each injection the animals were weighed. Five control rats received physiological saline only. Before the first injection a chest radiograph of each rat was obtained under light ether anaesthesia. Nine weeks after the start of the injections a second chest radiograph was obtained. Four weeks after the termination of the bleomycin injections, seven bleomycin-treated rats were placed in an airtight Perspex cage and exposed for 4 h to 50 % oxygen-enriched air. The flow was 4 litre min^{-1}, which was sufficient to prevent accumulation of carbon dioxide in the cage. The oxygen concentration was continuously measured with a Beckman oxygen analyser M11. One week after the hyperoxia treatment all rats were anaesthetized (i.p. injection of 1.0 or 1.4 ml of a 6 % solution of chloralhydrate for bleomycin-treated and controls, respectively) and a third chest radiograph obtained. Thereafter, the thorax was opened by a median incision and the trachea was cannulated. The left lung was ligated, excised and stored in ice cold physiological saline solution for the determination of SOD and GSH-Px activity. The right lung was perfused with pH 7.4 buffered 8 % formalin solution for 20 min at 20 cm H_2O pressure and prepared for histology. The lungs of experimental and control rats were processed concomitantly.

Histology

After fixation, two parts of the right lung, each of approximately 0.5 cm^3, were excised: a central part and a peripheral part of a "lower" lobe. Smaller pieces of each part were transferred into formalin for further fixation under vacuum and then embedded in glycolmethacrylate (Technovit 7100, Kultzer, Wehrheim, W. Germany). Two micrometre sections were cut and stained either with haematoxylin–eosin or with Bodia's reticulin solution. Each section was presented "blind" to the examiner who screened microscopically 10 fields for oedema, fibrotic changes, accumulation of intra-alveolar macrophages and the presence of type II pneumocytes in the alveolar wall, using a 400× magnification. Extension of oedema, number of cells and the thickness of the alveolar wall all were compared for the controls, bleomycin-treated and bleomycin plus oxygen-treated groups. The rating was based on the subjective interpretation of one of us (R.V.), using a 0–3 grading system. A grade 1 lesion for fibrosis consisted of thickening of the interstitial septum by infiltration of fibroblasts, whereas a grade 3 lesion corresponded to a well established scar with prominent deposition of collagen. Regarding macrophages and type II pneumocytes, a grade 1 lesion represented one or more foci of increased numbers of cells, whereas a grade 3 lesion corresponded to numerous foci or pronounced proliferation of cells which obscured normal lung architecture. Oedema grade 1 consisted of a slight thickening of alveolar septa, whereas grade 3 corresponded to extra-alveolar transudate.

Biochemical determinations

A 20% homogenate of excised pieces of the left lung (about 400 mg) was obtained with the aid of a glass homogenizer. Handling was performed at 4 °C. The homogenate was subjected to a two-step centrifugation procedure in an L3-40 Beckman centrifuge. The Ti50 rotor was used with Teflon adaptors for 2-ml cellulose nitrate tubes. The first step was a 30-min centrifugation at 13500 *g* directly followed in the same tube by 60 min at 131000 *g*. The supernatant was pipetted off, separated in three parts for the determination of SOD and GSH-Px activity and protein concentration.

The activity of SOD in the supernatant was assayed using a photochemical augmentation assay as described by Misra and Fridovich [15]. Briefly, the total reaction mixture was 3 ml containing riboflavin 13.3 μmol $litre^{-1}$ and dianisidin 200 μmol $litre^{-1}$ as well as 0.1 ml of the supernatant in a quartz cuvette. The cuvette was placed in an illumination box midway between two parallel 20-W Sylvania Gro-Lux fluorescent tubes. The increase in absorbance at 460 nm was measured after 10 min of illumination. Enzyme activity was expressed as units per mg of protein. As a standard a fresh preparation of bovine SOD (Sigma, 58254) was used containing 2700 units per mg of protein (E^1_{258}).

The activity of GSH-Px was assayed according to Lawrence and Burk [16]. Briefly, the total reaction mixture was 1 ml containing K_2HPO_4 50 mmol $litre^{-1}$ (pH 7.0), EGTA 1 mmol $litre^{-1}$, NaN_3 1 mmol $litre^{-1}$, NADPH 0.2 mmol $litre^{-1}$, GSH 1 mmol $litre^{-1}$, H_2O_2 1 mmol $litre^{-1}$, GSSG reductase 1 E.U. and 0.1 ml of supernatant. The reaction was started by adding the hydrogen peroxide. Oxidation of NADPH was recorded as change in the absorbance at 340 nm. Enzyme activity was expressed as μmol of NADPH oxidized per mg of protein per min.

Statistics

For comparison of mean responses in the three groups the two-sided Student *t* test was used. The *P* values given for the histological and biochemical observations are those of a randomization version of the *t* test [17].

RESULTS

Regular microbiological control demonstrated the efficacy of the barrier created by the laminar flow cabinet. No microbiological contaminants were discovered in the lungs of the rats of any group during the experimental period. The average body weights of the rats during this period are shown in figure 1. The weight gradually increased before bleomycin treatment, and continued to increase in the control group. Rats eceiving bleomycin showed a progressive derease of their body weight, which started immeliately after the first injection of bleomycin and ontinued even after the administration of bleomycin had been completed. The exposure to oxygen did not influence the slope of the curve. Bleomycin-injected animals finally reached a body weight below their starting value.

The chest radiographs obtained at the three

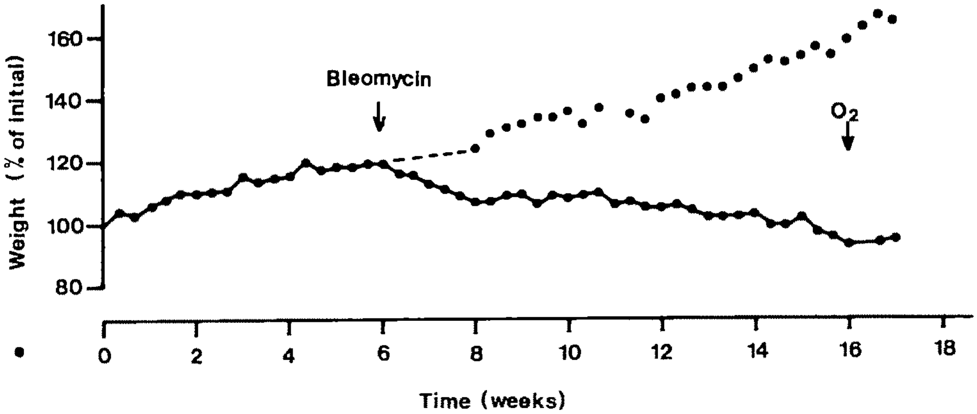

FIG. 1. Changes in mean body weight of 11 rats (●–●) after i.p. injection with bleomycin three times weekly for 6 weeks compared with those in five saline-injected controls (top: ● ●). Bleomycin injections started at the arrow. The second arrow points to the 4-h oxygen treatment.

TABLE I. *Data on lung histology of rats injected i.p. with bleomycin with or without oxygen treatment. Scores (mean ± SD) as defined in methods.* n = *No. animals.* *P < *0.05*; **P < *0.01*

Treatment	Macrophages	Pneumocytes II	Oedema	Fibrosis
None (*n* = 5)	0.3±0.2* **	1.3±0.2	0.3±0.2	0.3±0.2
Bleomycin (*n* = 4)	0.8±0.2*	1.2±0.2	0.3±0.2	0.2±0.2
Bleomycin+oxygen (*n* = 7)	1.1±0.1**	1.1±0.1	0.6±0.2	0.5±0.2
		ns	ns	ns

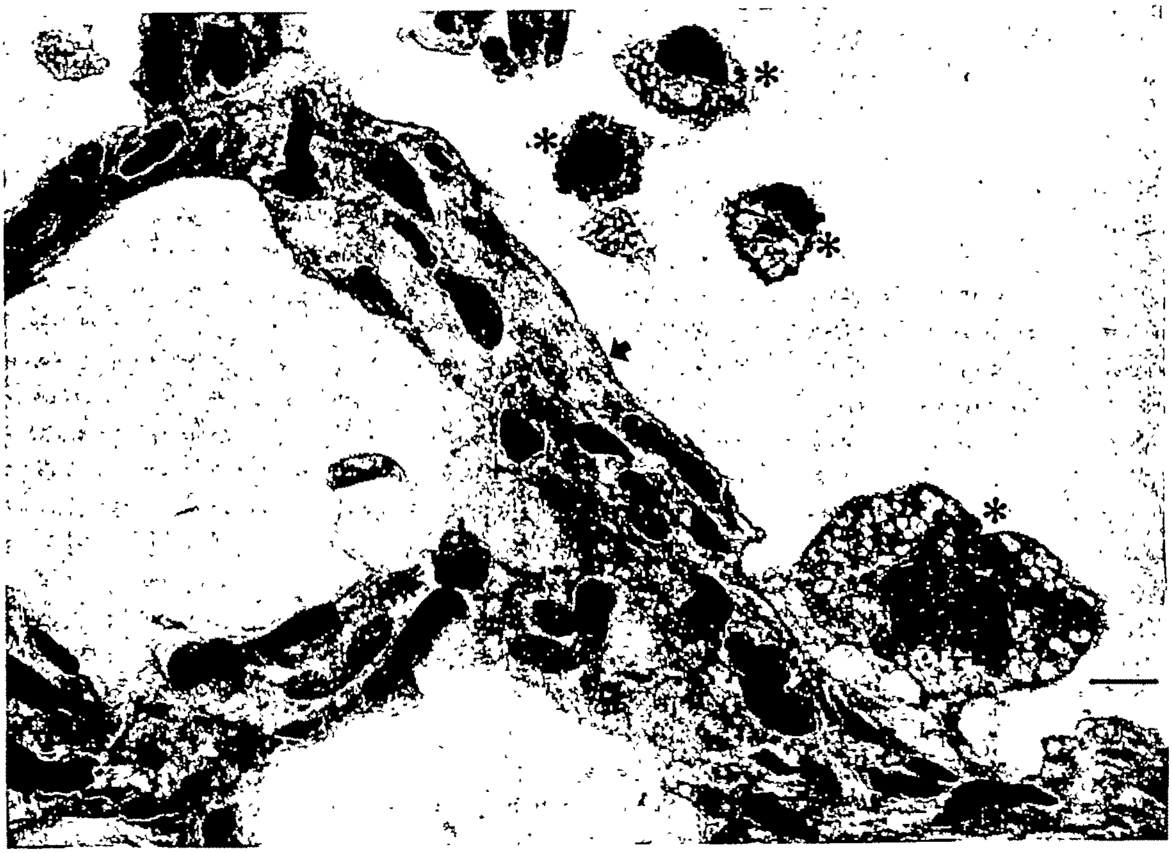

FIG. 2. Photomicrograph of lung showing thickening of alveolar wall as a result of the replacement of type I pneumocytes by type II pneumocytes. The accumulation of macrophages (*) within an alveolus is shown. Horizontal bar represents 7 µm.

different time points revealed no pulmonary abnormalities.

Lung histology

Histological examination of the lungs demonstrated the presence of a mild reaction in all three groups of rats; that is, the mean scores were around one or less (table I). Only the number of intra-alveolar macrophages was significantly increased in both the bleomycin-treated and the bleomycin+oxygen-treated rats as compared with controls (fig. 2). The number of macrophages in the bleomycin+oxygen-treated rats was increased significantly when compared with bleomycin-treated animals. Foci of increased numbers of type II pneumocytes in the alveolar wall were observed incidentally, but these did not differ significantly in the three groups. Likewise, the other two variables did not differ significantly in the three groups of animals.

TABLE II. *Effects of bleomycin injected i.p. with or without oxygen treatment on the activity of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) in rat lung. Mean values ± SD (number of assays)*

Treatment	SOD (u./mg protein)	GSH-Px (mol of NADPH/mg protein min^{-1})
None	6.5 ± 0.6 (4)	106 ± 15 (4)
Bleomycin	5.7 ± 0.8 (4)	89 ± 18 (4)
Bleomycin plus 50 % oxygen	6.2 ± 0.9 (5)	103 ± 17 (5)
	ns	ns

Lung biochemistry

The activities of the enzymes SOD and GSH-Px determined for the three different groups of rats are presented in table II. These did not differ significantly between the three groups.

DISCUSSION

Rats injected with bleomycin 10 mg/kg body weight i.p. three times weekly for 6 weeks, demonstrated (apart from the decrease in body weight) one alteration in the lung consistent with bleomycin toxicity—intra-alveolar accumulation of macrophages. Exposure to oxygen significantly influenced only the bleomycin-induced macrophage response. The activities of the enzymes GSH-Px and SOD remained unaltered. Chest radiographs were normal. Aiolfi and colleagues [18] observed more serious symptoms in rats: hyperplasia of type II pneumocytes, thickening of alveolar septa, obliteration of alveolar spaces, desquamative alveolitis and beginning of fibrillogenesis after injection of bleomycin 10 mg kg^{-1} i.p. every other day for 4 weeks. In addition, Tom and Montgomery [19] described more severe pulmonary changes in rats injected twice weekly with bleomycin 5 or 15 mg kg^{-1} i.p. Schurig and co-workers [20], using bleomycin 24 mg kg^{-1} s.c. three times weekly for 5 weeks, noted increases in alveolar macrophages and alveolitis, and interstitial pneumonitis and fibrosis in Sprague-Dawley rats. Similar effects were described for bleomycin in other animal species [21–23] after the parenteral administration of bleomycin.

Bleomycin-induced pulmonary damage was less marked in the present study. This, however, might create an adequate starting point for a superimposed oxygen response. Exposure to 50 % oxygen for 4 h, the approximate time span for anaesthesia during surgery, did not increase lung toxicity in our rats. Thus 50 % oxygen delivered for 4 h was not a complicating factor for bleomycin as regards the production of pulmonary toxicity in our rats. This finding is contrary to the results of a number of investigators who exposed animals to oxygen during, or subsequent to, treatment with bleomycin and obtained additive or potentiated toxic activity. Thus, Toledo and co-workers [4] found potentiation of bleomycin toxicity in mice that received 40 mg kg^{-1} s.c. twice weekly during 10 weeks of continuous exposure to 40 % oxygen. Exposure of hamsters to 70 % oxygen for 3 days subsequent to intratracheal administration of bleomycin decreased its LD_{50} from 7.3 to 2.3 mg kg^{-1} [6]. In all animals interstitial pneumonitis and fibrosis was present, and these were most severe in the oxygen-treated groups. Rinaldo, Goldstein and Snider [8] established increased interstitial injury in hamsters intratracheally instilled with bleomycin before exposure to either 60 or 100 % oxygen for 21 days. The degree of lung injury turned out to be related to the oxygen concentration and to be inversely related to the time elapsing between the instillation of the bleomycin and the start of the exposure to oxygen. Potentiation of bleomycin 50–100 mg kg^{-1}-induced lung damage by exposure to 70 % oxygen for 8 days was observed in mice if this exposure started immediately after the i.p. injection of bleomycin [5]. Finally, the combination of intratracheal bleomycin 6.0 mg kg^{-1} and 100 % oxygen for 48 h after instillation of the drugs resulted in synergistic alveolar toxicity in rats [24].

In all these studies the dose of oxygen delivered to the animals was greater than we used and exceeded the amount administered under clinical conditions. In most instances the dose of bleomycin was also greater; certainly, the dose reaching the lungs after intratracheal instillation of bleomycin was higher. It was determined that, after injection of bleomycin 10 mg kg^{-1} s.c. to mice, the maximal pulmonary concentration was less than 1% of the injected dose [25]. If a comparison is allowed with our rats injected with bleomycin i.p., approximately 0.02 mg reached the lungs after each injection. This dose was described to be effective in rats in causing several symptoms of lung toxicity [18] if injected every other day for 4 weeks. The total dose in this way exceeded that usually administered clinically. However, patients receive bleomycin by i.v. infusion, which is certainly more effective.

A possible explanation for the minor histological deviation from the control state observed in our study might be the induction of defense mechanisms during exposure to bleomycin. This, however, was not reflected in any increase in the activities of the antioxidant enzymes SOD and GSH-Px. This result questions the role of activated oxygen species in bleomycin toxicity. Phan and Fantone [26] presented evidence that the inhibition of bleomycin-induced pulmonary toxicity by lipopolysaccharide did not correlate with effects on antioxidant enzymes.

Our results with the dose of bleomycin used, in combination with the realistic oxygen exposure, are not totally unexpected in the light of the results of LaMantia, Glick and Marshall [11] obtained in man. These authors demonstrated that oxygen was not an adjuvant factor to bleomycin-induced toxicity. In fact, they confirmed the retrospective study of Douglas and Coppin [10] who found but one non-fatal case of pulmonary complications in 20 surgical patients previously treated with bleomycin in doses ranging from 150 to 570 mg and receiving, during surgery, oxygen concentrations up to 100%.

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MOLECULAR STRUCTURE OF FREE RADICALS AND THEIR IMPORTANCE IN BIOLOGICAL REACTIONS

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Although inorganic chemists have been aware of free radicals for many years [21] it is only recently that their importance in biochemistry and medicine has become more widely appreciated. The toxic nature of free radicals was firmly brought to the attention of the public by the recent Spanish cooking oil disaster. More than 100 people died and 20000 were injured following the ingestion of oil which, although sold as olive oil, was in fact rapeseed oil which had been "refined" to remove the aniline and acetanilide (added to imported rapeseed oil for industrial use only). During this treatment toxins had been generated which were capable of inducing free radical-mediated damage [51].

The purpose of this brief review is to provide anaesthetists with a simple introduction to the chemistry of free radicals and a reference to fundamental information which may not be readily available in a medical library. Although the emphasis is on oxygen, general considerations apply to a wide range of free radicals and it is certain that, with the continuing research in this field, the crucial role of these chemical species in normal and pathological biochemical processes will become increasingly apparent.

An awareness of the chemistry of free radicals, and the way in which damage to cells and tissues occurs, is crucial to the understanding of certain disease processes and their control by free radical scavenging drugs. Examples include the various manifestations of oxygen toxicity, a variety of inflammatory processes, reperfusion injury, cancer and the ageing process. Such a knowledge is particularly important for the anaesthetist who routinely uses agents known to be associated with the generation of free radicals (oxygen and halogenated hydrocarbons). For such an understanding it is first necessary to examine in some detail the covalent bonding between atoms and the effect of single electron transfer reactions. Examples of free radical reactions in biological systems will be given, with particular emphasis on reactions of interest to the anaesthetist.

Chemical bonding

In essence two types of chemical bond exist, ionic and covalent. *Ionic* bonding occurs when electropositive elements (for example, those from groups I and II of the periodic table, which lose their outermost electrons easily) combine with electronegative elements (for example, groups VI and VII elements, which tend to accept electrons easily). This interchange of electrons results in atoms gaining the most stable electron configuration—that is, that of the nearest inert gas (for example: $Na^+ \rightarrow Ne$, $Cl^- \rightarrow Ar$). Once formed, ions are held together by the electrical attraction of their opposite charge.

Covalent bonding requires the sharing of electrons between atoms. Atoms covalently bond because the potential energy of the molecule is lower than that of the atoms when they are present as separate entities. If sufficient energy is added to such a molecule the energy can be increased above that of the two separate atoms and the molecule will then dissociate (known as the bond dissociation energy). Either single (for example H_2), double (for example O_2) or triple (for example N_2) bonds can exist where the two atoms share 2, 4 or 6 electrons, respectively.

A single covalent bonding involving the sharing of electrons between two atoms (or molecules) A and B (signified either by: or - (A:B or A-B)) can break in three different ways:

$$A{:}B \rightarrow A{:}^- + B^+ \quad \text{heterolysis} \qquad (1.)$$

$$A{:}B \rightarrow A^+ + B{:}^- \quad \text{heterolysis} \qquad (2.)$$

$$A{:}B \rightarrow A^{\cdot} + B^{\cdot} \quad \text{homolysis} \qquad (3.)$$

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In (1.) and (2.), one of the atoms takes both electrons, resulting in the formation of ions. Fission of a single bond in this manner is known as heterolysis. Alternatively, each atom can take one electron, as in (3.). Known as homolysis, this reaction results in the generation of molecules, atoms or ions with an unpaired electron which are called free radicals (identified by $^{\cdot}$). In general, because of their unpaired electron status, free radicals are extremely reactive species, reacting rapidly with the majority of organic molecules which are resistant to the action of ions [41].

Free radical reactions

The main biological reactions in which free radicals participate are as follows:

$A^{\cdot} + B^{\cdot}$	$\rightarrow$ A-B	combination	(4.)
$A^{\cdot} + B\text{-}C\text{-}D^{\cdot}$	$\rightarrow$ A-B + C=D	disproportionation	(5.)
$A\text{-}B^{\cdot}$	$\rightarrow A^{\cdot} + B$	fragmentation	(6.)
$A^{\cdot} + B\text{-}C$	$\rightarrow A\text{-}B + C^{\cdot}$	radical transfer	(7.)
$A^{\cdot} + B{=}C$	$\rightarrow A\text{-}B\text{-}C^{\cdot}$	addition	(8.)

Generally, free radicals, particularly when formed in solution, react rapidly with many neighbouring molecular species. The radical half-life is usually very short and steady-state concentration is, therefore, low. However, in many biological systems, radicals are being continuously produced (for example, during oxidative phosphorylation).

There are, however, exceptions and some free radicals are more stable and, consequently, have longer half-lives. Indeed, free radicals were first identified because of a long-lived radical—the triphenylmethyl radical. Moreover, it is possible to keep otherwise unstable radicals for long periods of time by varying the conditions of storage such as pH and temperature.

Radical–radical reactions, (4.) and (5.), are extremely fast, but the rate depends on the square of the concentrations. Normally radical concentrations are extremely low so that reactions involving radical transfer (7.) and addition (8.) predominate. These reactions usually involve a chain process passing through initiation, propagation and termination stages. It is this process of radical propagation that is responsible for most of the damaging effects of free radicals (for example lipid peroxidation, described below).

The main biological targets of free radical attack are lipids, sulphydryl-containing proteins and DNA. Figure 1 shows the initiation of peroxidation in polyunsaturated fatty acids as a result of attack by reactive species resulting in a weakening of double bonds. Molecular rearrangement then occurs, forming a conjugated diene (-C=C-C=C-) which readily reacts with oxygen to form a peroxy radical (R-OO$^{\cdot}$). These radicals can cause hydrogen abstraction from another lipid molecule, with consequent weakening of the double bonds, resulting in propagation of the peroxidative process by a chain reaction. Membranes, being largely composed of unsaturated lipid and protein, are thus particularly vulnerable to oxidative attack. This process is familiar as it results in the rancidification of fat.

Proteins are also damaged by free radical reactions. It has been known for some time that many enzymes are rapidly inactivated by hyperoxia *in vitro* [25]. A general characteristic of such enzymes is their content of sulphydryl groups (-SH). These are easily oxidized, by molecular oxygen, free radicals or peroxides [29]. Conformational changes are then induced in the enzyme, resulting in decreased activity.

An example of the changes which occur in sulphydryl-containing compounds is shown where oxidation by the free radical A$^{\cdot}$ results in an intermediate thiyl radical which can then interact to form sulphur–sulphur bonds. Such a reaction is thought to explain the protective effect of thiol-containing compounds (such as cysteamine, methionine and n-acetylcysteine) in radiation injury, paracetamol poisoning and attack by radicals derived from oxygen, such as superoxide anion.

$$\begin{array}{l} \text{R-SH} + A^{\cdot} \rightarrow \text{R-S}^{\cdot} + \text{AH} \\ \qquad\qquad\quad + \\ \qquad\qquad\quad \text{R-S}^{\cdot} \rightarrow \text{R-S-S-R} \end{array}$$

Gluthathione is a sulphydryl-containing tripeptide which can be recycled by the interaction of the oxidized form with NADPH. This recycling of glutathione makes it particularly effective as a free radical scavenger.

$$\text{R-S-S-R} + \text{NADPH} + \text{H}^{+} \rightarrow 2\text{R-SH} + \text{NADP}^{+}$$

Free radical damage to nucleic acids and nucleotides has been extensively studied with particular reference to the effects of ionizing radiation and carcinogenesis [19, 30, 31]. It would seem that most destruction occurs by radical attack of the pyrimidine to deoxyribose bond,

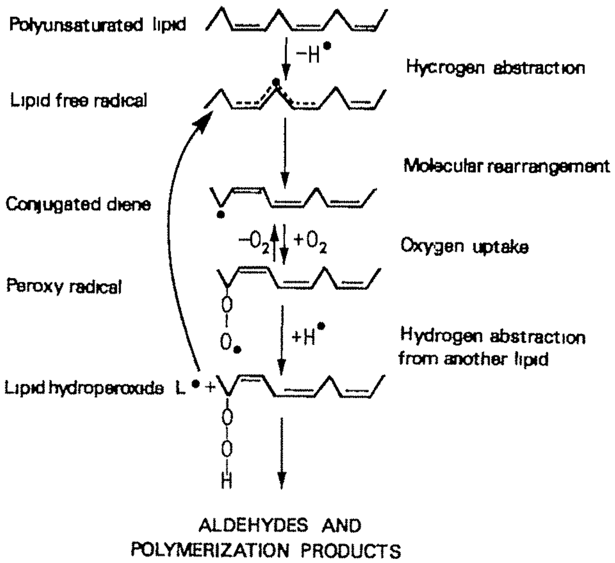

FIG. 1. Initiation and propagation reactions of lipid peroxidation.

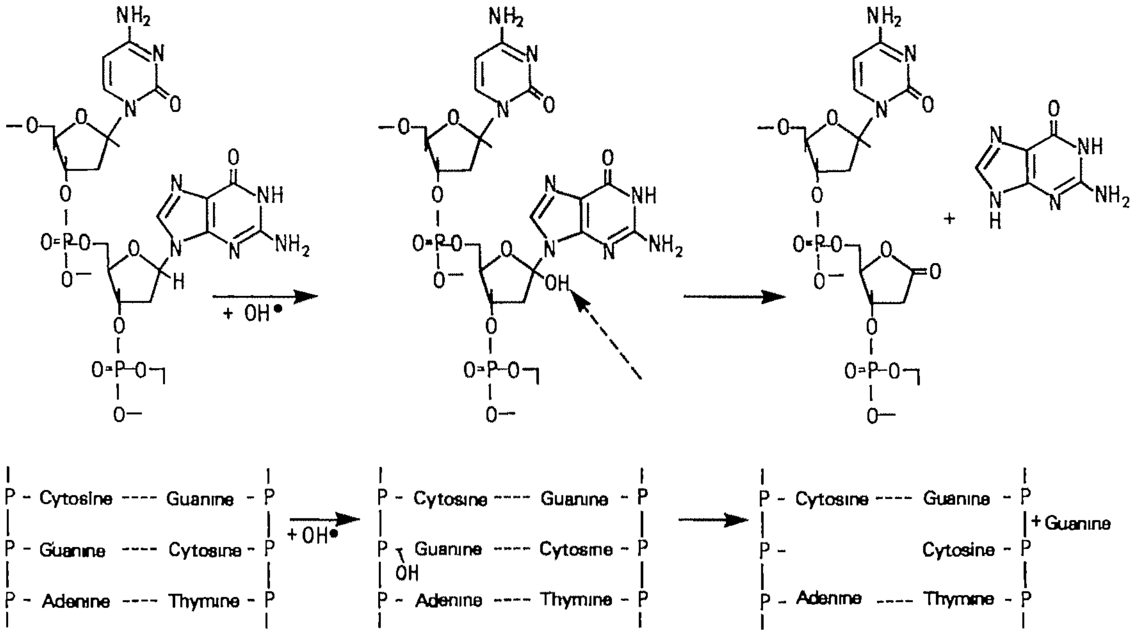
NH_2
N
O
+ OH•
NH
OH
H
+
P - Cytosine ---- Guanine - P
P - Guanine ---- Cytosine - P
P - Adenine ---- Thymine - P
+OH•
P - Guanine ---- Cytosine - P
OH
P -
Cytosine - P
+ Guanine

FIG. 2. One possible mechanism for hydroxyl radical-induced single strand scission of DNA. The lower figure illustrates the effect that this would have on the double strand DNA.

with breakage of the sugar–phosphate bond and liberation of free bases from the nucleotides (fig. 2).

It is now thought that the reactivity of a radical in an isolated chemical system is a relatively unimportant predictor of the degree of biological damage that may result from the exposure of the intact organism to that radical. An unstable radical will be more likely to interact with itself and any other molecule it meets, whereas a more stable radical may produce more damage by reacting only with certain, and perhaps crucial, chemical species. It is believed that these latter sites of interaction are molecules of major biological significance (for example, the amino acids which determine the conformational structure of proteins).

Protective systems

To prevent damage arising from excess free radical concentrations, a variety of protective mechanisms are used. These essentially fall into two groups:

(1) *Preventative or primary antioxidants.* These reduce the rate of initiation of free radical chain reactions by decreasing the concentration of free radicals available to react with cell components.

(2) *Chain-breaking or secondary antioxidants.* These trap the chain propagating radicals, thus arresting the destructive chain reactions at an early stage.

There are five groups of free radical scavenging agents which can be used in biological systems:

(1) Water soluble compounds, for example ascorbic acid and the sulphydryl containing glutathione (γ-glutamyl-cysteinyl-glycine).

(2) Naturally occurring fat soluble compounds, for example α-tocopherol and β-carotene.

(3) Substances bound to high molecular weight materials, for example the sulphydryl-containing proteins.

(4) Exogenous compounds, for example the food antioxidants (butylated hydroxytoluene, propylgallate, ethoxyquin and nordihydrogaurietic acid) and drugs such as the phenothiazines.

(5) Enzymes. There are three enzymes intimately concerned with the detoxification of oxygen-derived free radicals:

Superoxide dismutase catalyses the reaction of two superoxide anions ($O_2^{\cdot -}$) with the consequent formation of hydrogen peroxide:

$$O_2^{\cdot -} + O_2^{\cdot -} + 2H^+ \rightarrow H_2O_2 + O_2$$

Two enzymes guard against damage from hydrogen peroxide: catalase and glutathione peroxidase. *Catalase* is highly specific and has appreciable activity only for hydrogen, methyl and ethyl hydroperoxides:

$$2H_2O_2 \rightarrow 2H_2O + O_2$$

Glutathione peroxidase has a more general action and catalyses the reduction of many hydroperoxides (R-OOH) by reduced glutathione (G-SH):

$$\text{R-OOH} + 2\text{G-SH} \rightarrow \text{R-OH} + \text{G-S-S-G} + H_2O$$

(Note that R-OOH is different from an organic acid R-COOH such as acetic acid CH_3-COOH.)

Although deficiency of either catalase or glutathione peroxidase has been reported in man, only anaerobic organisms and a very few aerobic bacteria are without superoxide dismutase.

Oxygen and oxygen-derived free radicals

Molecular oxygen (dioxygen) is a stable biradical, as it has an unpaired electron in the outer shell of each constituent oxygen atom. This may at first seem somewhat surprising, as the total number of electrons in molecular oxygen (16) would suggest that each is fully paired. However, a more detailed examination of molecular electron configuration (given in the Appendix) will reveal that this cannot be so. Moreover, largely as a result of the constraints imposed by energy conservation, the two unpaired electrons of molecular oxygen spin in the same direction (parallel spin). It is this latter fact that explains the paramagnetic properties of molecular ground state oxygen. Moreover, it also prevents it acting as a free radical since, if these electrons spin in opposite directions (as in singlet oxygen), a much more reactive molecule results.

Oxygen readily accepts electrons from other molecules; that is, it is a powerful oxidizing agent, and each molecule of oxygen can accept a total of two pairs of electrons. However, pairs of electrons cannot be accepted at the same time, since both of these electrons would have to be in parallel spin to fit into the free electron orbitals. Such a pair of electrons cannot exist, because any pair must necessarily have opposite spins in accordance with basic chemical principles. The so-called spin restriction forces oxygen to accept only one electron at a time and means that oxygen reacts only slowly with many non-radical compounds.

More reactive forms of oxygen can, however, be generated. With the input of energy, the two parallel spinning electrons can take up antiparallel spins with the formation of two possible forms of what is known as singlet oxygen, $^1\Delta gO_2$ (energy level of 22.4 kcal above ground state) or $^1\Sigma g^+$ (37.5 kcal above ground state). In both of these singlet forms spin restriction has been removed and the oxidizing ability of oxygen is greatly

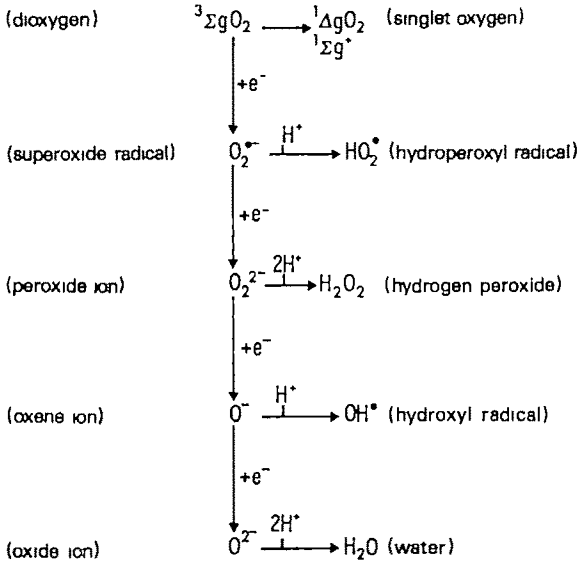

FIG. 3. Products derived from the successive one electron reduction of dioxygen.

increased. Alternatively, electrons can be added to ground state molecular oxygen singly (fig. 3).

The addition of an electron to ground state dioxygen (giving what is known as the one electron reduction product) forms the free radical superoxide anion ($O_2^{\cdot -}$). In biological systems the two-electron reduction product of ground state oxygen is hydrogen peroxide and the four-electron product is water. This reaction is occurring continuously within the cell during oxidative phosphorylation. Some oxidases, such as cytochrome oxidase, reduce oxygen to water without detectable formation of free radical intermediates, apparently producing a one step four-electron reduction of oxygen to water [10]. However, it is thought that oxygen derived radicals are formed, but are normally bound to active sites within the enzyme and, therefore, remain "hidden" from other intracellular components [7].

Although ground state dioxygen is an oxidizing agent (it accepts electrons readily), superoxide anion mainly undergoes reducing reactions (it readily donates an electron).

Hydroxyl radical and hydrogen peroxide

It would seem unlikely that $O_2^{\cdot -}$ is responsible for all the damage seen in experimental systems involving oxygen-derived free radical species, and it is well known that hydroxyl radical ($OH^{\cdot}$) is much more reactive than $O_2^{\cdot -}$. Reactions which produce $OH^{\cdot}$ do occur in cells. One such reaction (known as the Haber–Weiss reaction), which was first described in a purely chemical system, involves the reaction of hydrogen peroxide with $O_2^{\cdot -}$:

$$H_2O_2 + O_2^{\cdot -} \rightarrow O_2 + OH^- + OH^{\cdot}$$

Because of the low reaction rate constant and the small steady state $O_2^{\cdot -}$ concentration, this reaction is unlikely to occur *in vivo* [24, 36]. However, the rate constant can be greatly increased by trace concentrations of transition metals (for example copper and iron). This is known to occur *in vivo* (the Fenton reaction) and, similarly, involves transition metals and hydrogen peroxide thus:

$$Fe^{3+} + O_2^{\cdot -} \rightarrow Fe^{2+} + O_2$$

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^{\cdot} + OH^-$$

The importance of transition metals in free radical generation within biological systems has only recently been appreciated and would suggest that chelators, which bind such metals and render them inactive as catalysts, may be useful therapeutic agents in some disease processes.

Irradiation and the oxygen effect

The effects of ionizing radiation in an aqueous system are shown in reactions 1–4 below. The subsequent interactions with oxygen and the products $H^{\cdot}$ and e^- (reactions 5–7) result in an enhancement of the effects of irradiation at high partial pressures of oxygen [20, 22]. This principle has been used in tumour radiotherapy.

1. $H_2O \rightarrow H_2O^+ + e^-$
2. $H_2O + e^- \rightarrow H_2O^-$
3. $H_2O^+ \rightarrow H^+ + OH^{\cdot}$
4. $H_2O^- \rightarrow H^{\cdot} + OH^-$
5. $O_2 + H^{\cdot} \rightarrow HO_2^{\cdot}$
6. $O_2 + e^- \rightarrow O_2^{\cdot -}$
7. $O_2^{\cdot -} + H^+ \rightarrow HO_2^{\cdot}$
8. $2HO_2^{\cdot} \rightarrow H_2O_2 + O_2$

Oxygen toxicity and irradiation are in many ways similar and Gerschman and colleagues [18] were the first to propose that oxygen-derived free radicals are responsible for the pathophysiology of oxygen poisoning. This suggestion has led to the investigation of many radioprotective substances as possible therapeutic agents for oxygen toxicity

[11, 28, 58], but as yet no agent has been found to be of particular benefit.

Ozone and the oxides of nitrogen

Other important and powerful oxidants are ozone and nitrogen dioxide, both common environmental pollutants. The molecular structure of ozone is such that the O–O bonds (bond distance 1.26 Å) are intermediate in character between single and double bonds as the bond distance of HO-OH (single bond) is 1.49 Å and that of oxygen O,O (double bond) is 1.10 Å [44]. Tetratomic oxygen (O_4) also exists, but is present in appreciable quantities only in liquid and solid oxygen [32]. Little is known about the reactivity of this molecule, which is made up of two O_2 molecules held together by forces which are intermediate between electron sharing and Van der Waals electrostatic bonds.

Nitric oxide and nitrogen dioxide are free radicals, and are capable of directly causing lipid peroxidation by attacking unsaturated carbon bonds. Nitric oxide reacts with oxygen to form nitrogen dioxide and both oxides can react with hydrogen peroxide (readily available *in vivo*) to produce hydroxyl radicals. The higher oxides of nitrogen may contaminate nitrous oxide used in anaesthesia and some of their effects are attributable to free radicals [38, 50]. Radiation chemists routinely generate hydroxyl radical by the reduction of nitrous oxide by aqueous electrons from gamma irradiation:

$$N_2O + e^- \rightarrow OH^{\cdot} + OH^- + N_2$$

Another major environmental pollutant is smoke, including cigarette smoke. Inactivation of alpha-1-antiproteinase by the oxidants in smoke diminishes the antiproteinase defenses of the lung and is suggested to be the method by which excess protease activity results in the pathogenesis of emphysema [8]. In a similar manner, oxidants released from stimulated leucocytes could result in inactivation of antiproteinases.

Bipyridyl herbicides and paracetamol

These commonly ingested poisons are thought to produce damage by free radical intermediates. The bipyridyl compounds paraquat and diquat easily cross membranes and readily accept electrons from the electron transport chain of either the chloroplast or the mitochondrion, with the formation of the bipyridyl radical ($BP^{\cdot +}$). In the presence of oxygen, superoxide anion is rapidly formed, with the consequent production of hydrogen peroxide and hydroxyl radical [47]:

$$BP^{2+} + e^- \rightarrow BP^{\cdot +}$$

$$BP^{\cdot +} + O_2 \rightarrow BP^{2+} + O_2^{\cdot -} \text{ (Note } BP^{2+} \text{ is recycled).}$$

The type I pneumocyte of the lung is unfortunate in both accumulating paraquat or diquat against a concentration gradient as well as having the greatest P_{O_2} in the body.

In similar fashion paracetamol is metabolized via a free radical intermediate which is capable of causing direct cell damage [15].

Halogenated hydrocarbons

Carbon tetrachloride (CCl_4), chloroform ($CHCl_3$) and halothane ($CF_3CHBrCl$) are halogenated hydrocarbons which form free radical intermediates during biotransformation. When they are metabolized by the cytochrome P450 system homolytic fission occurs, with the generation of free radicals which then undergo chain propagation reactions with other anaesthetic molecules, lipids, thiols or oxygen.

$$CCl_4 \rightarrow Cl^{\cdot} + CCl_3^{\cdot} \rightarrow CCl_3O_2^{\cdot}$$

$$CHCl_3 \rightarrow H^{\cdot} + CCl_3^{\cdot}$$

$$CF_3CHBrCl \rightarrow Br^{\cdot} + CF_3CHCl^{\cdot}$$

Alternatively, an electron may be added to the reaction from the mixed function oxidase P450 system:

$$CF_3CHBrCl + e^- \rightarrow Br^- + CF_3CHCl^{\cdot}$$

These changes have been particularly studied with carbon tetrachloride and halothane, which are both capable of causing centrilobular hepatic necrosis in certain animal models. It is probably the mechanism which results in the enhanced hepatotoxicity seen with many of these compounds following stimulation of P450 activity with phenobarbitone [33, 39, 40, 45, 55].

Oxygen toxicity

Although oxygen therapy is clearly beneficial in many clinical settings, it has long been recognized that it also carries a risk of tissue damage. This action was first demonstrated by Paul Bert [5] using hyperbaric oxygen and was later found also at normobaric pressures by Smith [46].

The lung is exposed directly to the highest partial pressures of oxygen and atelectasis, oedema, alveolar haemorrhage, fibrin deposition and thickening of alveolar membranes can be demonstrated in animals following exposure to 80–100% oxygen for 2 days. The cells most clearly damaged by oxygen are the capillary endothelium and the alveolar type I epithelial cells.

Currently, the most popular theory to explain the pathology of oxygen toxicity is that specific damage occurs as a result of the intracellular production of oxygen-derived free radicals in excessive concentrations which overwhelm the natural defences of the cell. Support for this theory comes from two sources. First, it has been demonstrated that mitochondria release excess superoxide anion under hyperoxic conditions [56]. Second, it is possible to produce enhanced endogenous antioxidant activity by treatment of rats with 85% oxygen; these animals will then tolerate exposure to 100% oxygen for prolonged periods [12].

Retrolental fibroplasia

This condition, which can lead to blindness, is believed to be a complication of the use of an increased partial pressure of oxygen in premature infants [43]. There are two possible aetiologies for this disease: vasoconstriction resulting in ischaemia, and increases in the concentrations of oxygen-derived free radicals. In addition to the increased partial pressure of oxygen within the eye as a result of oxygen therapy, singlet oxygen is generated as a result of u.v. irradiation. However, retrolental fibroplasia still occurs, even with the closely monitored administration of oxygen, and it is now considered that "excessive" oxygen is only one factor in what is a disease with a multifactorial aetiology [16, 34]. Nevertheless, there is evidence that the administration of tocopherol may reduce the risk of developing severe retrolental fibroplasia [26].

Reperfusion injury

It is now becoming apparent that free radicals may play some role in the pathology of ischaemia and reperfusion injury [35]. It has long been accepted that the major adverse changes seen in ischaemia are caused by the depletion of adenosine triphosphate (ATP) and an increase in H^+ during the period of hypoxia. However, another possible explanation is that the deleterious effects actually occur during reperfusion and are the result of the generation of free radicals from dioxygen as a result of oxidation of the accumulated reduced compounds [17, 42] (fig. 4). Xanthine oxidase reduces oxygen to $O_2^{\bullet -}$ which is then released into the intra- and extracellular fluid. Xanthine oxidase is thought to be generated from xanthine dehydrogenase (an enzyme which transfers electrons from substrates on to NAD^+ rather than O_2) during periods of ischaemia, presumably by the action of proteolytic enzymes [4]. There is also an increased concentration of hypoxanthine (another substrate of xanthine oxidase) during ischaemia (fig. 4). Allopurinol, a xanthine oxidase inhibitor, has been shown to prevent ischaemic damage [42].

Currently, there is much interest in the possible use of antioxidants and free radical scavengers in the prevention of reperfusion injury during cardiopulmonary bypass, in an attempt to improve myocardial function following arrest. Protection of mechanical and subcellular function has been reported by Stewart and co-workers [48] using a cardioplegic solution of superoxide dismutase, mannitol and potassium chloride in dogs on cardiopulmonary bypass, while other workers have found significant improvement in patients undergoing bypass when a single oral dose of vitamin E (2000 iu) was given 12 h before operation [9].

Another area where free radicals generated as a result of ischaemia are important is in the field of transplantation, where much current research is directed at limiting the effects of free radical-induced damage by treatment before and after the period of organ ischaemia [49].

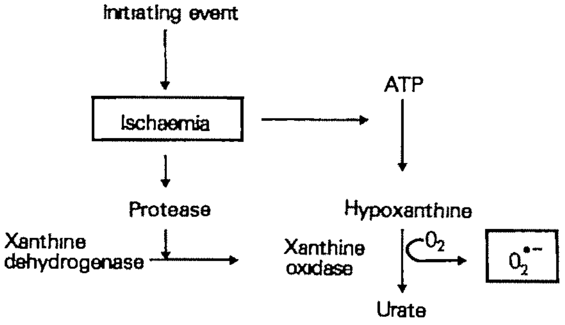

FIG. 4. The generation of superoxide anion ($O_2^{\bullet -}$) resulting from ischaemia and reperfusion. Ischaemia permits the conversion of xanthine dehydrogenase to the oxidase form, and provides an excess of substrate (purine metabolites) for this enzyme. Reperfusion and reoxygenation then allows the xanthine oxidase reaction (which requires oxygen) to occur with production of superoxide anion.

ARDS and multiple organ failure

Adult respiratory distress syndrome (ARDS) is a form of acute lung injury characterized by hypoxaemia refractory to treatment, together with a high permeability pulmonary oedema. The pathogenesis of ARDS is complex and involves, probably, many mechanisms including microthrombus formation [23], prostaglandin release [6] and intrapulmonary sequestration and stimulation of polymorphonuclear leucocytes [13]. As described below, stimulated white cells will release both oxygen-derived free radicals and connective tissue proteases. Large numbers of white cells have been identified in bronchoalveolar lavage fluid obtained from ARDS patients and this fluid has also been found to contain myeloperoxidase and collagenase (released from white cells) [57]. Further characteristics of ARDS, high pulmonary artery pressure and vascular resistance, can also be attributed to increased toxic oxygen metabolites. In an experiment on isolated perfused rabbit lungs Tate and colleagues [53] have shown that such metabolites stimulate thromboxane production, by enhancing the metabolism of arachidonic acid, and thus cause vasoconstriction.

Plasma lipid peroxide concentrations have been shown to be increased in critically-ill patients in Intensive Care Units, and this is associated with significant reductions in plasma alpha-tocopherol concentrations [52]. The highest lipid peroxide concentrations were found in septic patients and, in particular, those who developed disseminated intravascular coaggulation (DIC). The authors suggest that antioxidant therapy with, for example, alpha-tocopherol may prevent peroxidation in patients liable to develop DIC and multiple organ failure.

If antioxidants are to be used in conditions such as ARDS and multiple organ failure, then tissue-specific targeting may become important. In this regard it has been suggested that polyethylene glycol (PEG) conjugation with antioxidants may be more effective than liposome encapsulation [37]. Delivery of antioxidants conjugated to PEG has been shown to be improved and their half-lives prolonged over that with liposome encapsulation.

Biologically useful radical reactions

All reactions discussed so far have been deleterious; however, free radical reactions within cells are often useful, and some are essential for normal cell function. Once the polymorphonuclear leucocyte is attracted to sites of infection and stimulated to destroy the foreign materials, it undergoes a series of oxygen-dependent reactions with the release of superoxide radical [1, 2]. Individuals with chronic granulomatous disease lack the enzyme NADPH oxidase and, therefore, the capacity to generate superoxide radical. Such patients have an abnormal susceptibility to bacterial infections [3, 27]. It is possible that some inflammatory diseases (for example rheumatoid arthritis, adult respiratory distress syndrome and autoimmune disorders) are caused by the excessive or inappropriate stimulation of leucocytes, with the consequent release of high concentrations of superoxide radical [14, 54].

There are many other important reactions where free radical intermediates are essential for normal cell function, including the formation of deoxyribonucleotides from ribonucleosides, oxidation, carboxylation and hydroxylation reactions and prostaglandin metabolism.

CONCLUSIONS

With greater understanding of the role of free radical reactions in disease processes, it should be possible to investigate more rational approaches to therapy. Such therapy would be directed towards reducing free radical concentrations by either preventing their formation or preventing their reaction, by scavenging, with other molecules of importance within the cell.

APPENDIX

Structure of the atom

Electrons possess a negative charge and must, therefore, have energy to prevent them from being pulled into the positively charged nucleus. They exist in shells (1, 2, 3...7) and move around the nucleus in one of four orbital patterns, spinning in either direction. Each of these features (except for spin direction) is related to a particular energy level. The s orbital is spherical, but the others (p, d and f) can be described in one of three different planes (x, y and z) each with a maximum of two electrons around the nucleus. The p orbit, the only one to concern us here apart from s, is shown in figure 5.

The notion of an electron having a discrete position (for example following a definite orbit) has now been replaced by the Schrodinger concept of a probability distribution which describes how the density of the charge cloud is distributed in space. This concept allows the charge distribution to be calculated for atoms as well as molecules, where electrons occupy orbitals centred on both nuclei.

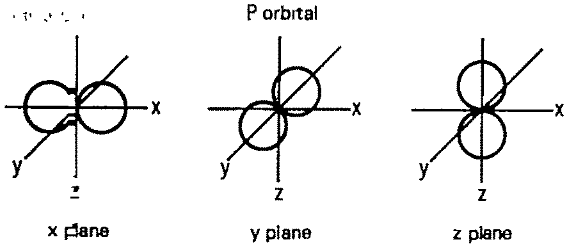

FIG. 5. The three planes of the p orbit electrons.

The electronic structure of any atom or molecule may be defined by taking account of the following factors:

(1) Orbitals are filled in order of increasing energy.

(2) Each orbital may hold only two electrons with opposite spins (the Pauli exclusion principle).

(3) Where several orbitals of equal energy are available (for example the 3p orbitals of shell 2) the electrons fill each singly, keeping their spins parallel, before spin pairing occurs. This is known as Hund's rules: as far as possible electrons avoid being in the same orbital, and electrons in different orbitals of the same energy have parallel spins.

Structure of the molecule

In the case of molecules, electrons can "interact" with each other either "constructively" or "destructively" and are said to be either in bonding orbitals where there is an accummulation of electron density in the region between the two nuclei (this has the effect of reducing their internuclear repulsion); or in antibonding orbitals (signified by *) where the probability of finding an electron between the nuclei is zero. In the absence of electrons between the nuclei, the internuclear repulsive force has full effect (fig. 6).

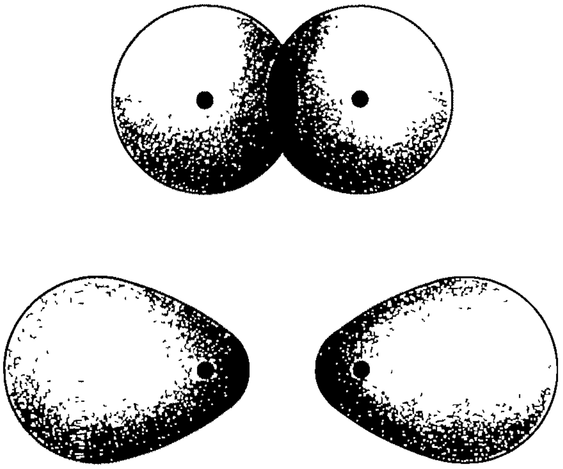

FIG. 6. Bonding and antibonding orbitals. In the upper figure the s electron cloud from each atom are interacting in such a way as to provide a high probability of finding a negative charge between the two nuclei. This reduces the internuclear repulsion to zero and the electrons are said to lie in a bonding orbital (σ). In the lower figure there is a zero probability of finding a negative charge between the two nuclei and the internuclear repulsive force is maximum; an antibonding orbital (σ^*).

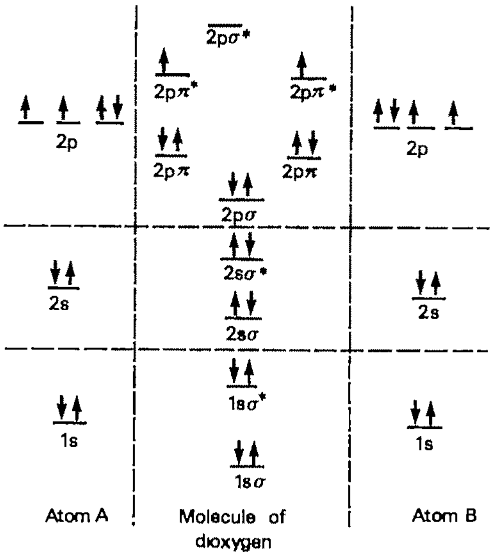

FIG. 7. The detailed electron structure of dioxygen. Two oxygen atoms (Atom A and Atom B) are shown on either side of the molecule of dioxygen which results from their combination.

The s atomic orbital electron density is symetrical and, in a molecule, two such electrons can interact to form molecular orbitals known as σ which may be either bonding (sσ) or antibonding (sσ^*). Similarly, two p_x orbital electrons can interact to form molecular orbitals like those formed by s atomic orbitals and these are known as pσ or pσ^*. The p_x or p_y atomic orbitals cannot enter into σ bonding, but can overlap sideways to form π bonds (again either bonding (pπ) or antibonding (pπ^*)). Electrons enter each of these molecular orbitals in strict order of energy level, filling the lower levels before entering higher levels. Energy levels increase in the order $1s\sigma < 1s\sigma^* < 2s\sigma < 2s\sigma^* < 2p\sigma < 2p\pi < 2p\pi^* < 2p\sigma^*$.

Structure of the oxygen molecule

The oxygen atom has eight electrons distributed as follows: $1s^2 2s^2 2p^4$ (fig. 7). When two atoms join to form diatomic oxygen (dioxygen) the molecular electron distribution can be calculated from the rules given above. The four 1s electrons (two from each atom) fully occupy both 1s bonding and 1sσ^* antibonding molecular orbitals. The four electrons in the next shell which have s atomic orbitals occupy 2sσ and 2sσ^* molecular orbits. Eight outer electrons are now left; two exist in $2p_x$ orbitals making a 2pσ bonding orbit. The 2pσ^* antibonding orbitals are not occupied because they are of higher energy level than both the pπ and pπ^* molecular orbitals. The $2p_x$ and $2p_y$ atomic orbitals can overlap laterally to give $p_x\pi$ and $p_y\pi$ bonding molecular orbitals. The remaining two electrons must occupy the next highest molecular orbital in energy; there are two such orbitals $2p_x\pi^*$ and $2p_y\pi^*$, and by Hund's rule, each must receive one electron. Since the presence of one electron in each of these molecular orbitals cancels one of the 2pπ bonding orbitals, the two oxygen atoms are effectively joined by a double bond. Molecular oxygen therefore, has two unpaired electrons in the outer shell occupying $2p_x\pi^*$ and $2p_y\pi^*$ orbitals (fig. 7).

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SAFE USE OF PROPOFOL IN A PATIENT WITH ACUTE INTERMITTENT PORPHYRIA

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L. C. FUITH

SUMMARY

On two occasions a patient suffering from acute intermittent porphyria (AIP) was anaesthetized with propofol as the sole agent. The concentrations of urinary porphobilinogen, porphyrins and porphyrin precursors did not exceed preoperative values, and no exacerbation of the disease was noted.

The porphyrias are a group of diseases characterized by defects in porphyrin metabolism. Only acute intermittent porphyria (AIP), variegate porphyria (VP) and hereditary copro-porphyria can lead to acute attacks. These may be caused by drugs, especially barbiturates. Other anaesthetic agents such as Althesin, diazepam and ketamine may also induce life threatening porphyric attacks [1]. This case report describes the safe use of propofol on two occasions during the anaesthetic management of a patient suffering from acute intermittent porphyria.

CASE HISTORY

A 43-yr-old female (weight 52 kg, height 1.65 m) was admitted to hospital with a stage IIb cervical carcinoma (parametrial infiltration [2]). The patient had previously undergone surgery for appendicectomy and tonsillectomy at 8 and 11 yr respectively, without major anaesthetic complications. In 1967 she delivered a son who died after 6 months.

In 1969 a live, healthy female infant was delivered by Caesarean section, for which anaesthesia had been induced with thiopentone. The patient remembers muscle weakness in her right arm, which persisted for several days.

Her first acute porphyric attack occurred in 1974. No precipitating factor was identified. In the following 10 years three further acute episodes occurred, each necessitating admission to hospital. Two of these attacks followed influenzal illnesses.

Each attack was characterized by abdominal pain, general muscle weakness, and increases in the concentrations of urinary porphyrins and porphyrin precursors. A positive diagnosis was based on the porphyrin chromatogram, which was typical for AIP [3].

On this admission the patient had no clinical symptoms of porphyria, but did have signs of a chronic distal neuropathy; the concentrations of urinary porphobilinogen, porphyrins and porphyrin precursors were increased (table I). All other laboratory findings, including tests of hepatic function, were normal.

Combined percutaneous and high-dose rate afterloading radiation (HDR) therapy using an afterloading machine (Selectron type with cobalt 60, 500 mCi/pellet) was planned. In order to position the radiation applicator it was necessary to dilate the cervical os under general anaesthesia. The patient was not premedicated. Anaesthesia was induced with propofol 100 mg i.v. using a forearm vein. After 20 s the patient lost consciousness, and ventilation was assisted with 100 % oxygen. The gynaecological procedure lasted 7 min. Eleven minutes after the injection of propofol the patient was completely responsive, fully orientated and co-operative. The subsequent postoperative period was uneventful. The 24-h

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TABLE I. *Twenty-four-hour urinary excretion of porphyrins and precursors*

	Anaesthetic	Before operation	After operation	Normal range
Delta-aminolaevulinate (mg)	1	31.2	28.5	0–2.5
	2	28	29.1	
Porphobilinogen (mg)	1	36.4	30.4	0–1
	2	32.6	31.4	
Uroporphyrin (μg)	1	14.9	5.8	3–15
	2	12.2	8.1	
Total porphyrins (mg)	1	611.6	532.8	
	2	655.6	283.8	

urinary excretion of porphobilinogen and precursors remained close to the preoperative values (table I).

Two weeks later a further radiation treatment was planned. As before, anaesthesia was induced using propofol 100 mg i.v. An increment of 60 mg was necessary as the positioning of the radiation applicator proved to be more difficult than on the first occasion. Recovery was complete and no porphyric symptoms appeared. Once again, porphyrin excretion remained unchanged.

DISCUSSION

Acute intermittent porphyria is characterized by a decrease in the activity of uroporphyrinogen-synthase (UPG-S) [4]. As a result, haem production decreases. Reduced haem enhances the activity of delta-aminolaevulinate synthase (ALA-S) by negative feedback. Increased amounts of delta-aminolaevulinic acid, porphobilinogen and porphyrins are produced. Porphyrinogenic drugs act by further enhancing ALA-S activity by a variety of mechanisms [5]. Clinical symptoms of the acute attack are closely related to the nervous system. Abdominal pain, constipation, muscle weakness, ascending paralysis, encephalopathy, psychosis, tachycardia and hypertensive crisis are most common.

For positioning of the radiotherapy applicator a short-acting anaesthetic with rapid recovery is necessary, so that treatment can begin at once. During the following radiation time (generally about 5 min) the patient must be awake and fully responsive, since she is monitored indirectly by closed-circuit television.

Spinal anaesthesia is usually used for this purpose. However, little guidance is available on the application of regional anaesthesia to patients with porphyria, and general anaesthesia was considered safer in this subject. Furthermore, the patient suffered from chronic distal neuropathy and this provided a further contraindication to regional anaesthesia [6, 7].

The porphyrinogenicity of propofol has been compared with that of phenobarbitone, which is a powerful porphyrin inducer [8]. The effects of both drugs upon delta-aminolaevulinate synthase activity were measured quantitatively in rat liver. Propofol did not enhance activity of this enzyme and the authors concluded that it would probably be a safe drug for patients with porphyria. The results of that study led to the choice of propofol in our patient.

Although two administrations of propofol to this patient were entirely uneventful, recommendations for using propofol in AIP patients must be very guarded until further successful administrations are reported.

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ASSESSMENT OF A NEW NASOPHARYNGEAL AIRWAY

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SUMMARY

A new design of nasopharyngeal airway, which incorporates an introducer, was compared with a standard red rubber airway. The new airway was more frequently of the correct length, but the incidence of bleeding (12.5%) was not significantly different from that with the red rubber airway (27.5%).

Maintaining the patency of the upper airway during anaesthesia may necessitate the insertion of a nasopharyngeal rather than an oropharyngeal airway. To be effective, the distal end of any nasopharyngeal airway should protrude beyond the pharyngeal border of the soft palate, but should not pass more distally than the epiglottis. Bleeding and trauma to the nasal mucosa have been noted in isolated incidents after nasotracheal intubation [1, 2], but the incidence of bleeding associated with the insertion of a nasopharyngeal airway has not been reported.

Recently, a new design of nasopharyngeal airway, the Linder, has been introduced. The Linder airway (fig. 1) is supplied with a Bubble-Tip introducer which consists of a one-way valve, a 20-cm hollow tube and a distal balloon (fig. 2). With the introducer in the airway, air (usually 4–5 ml) is injected through the one-way valve until the balloon is inflated to the approximate dimensions of the outside diameter of the tube (fig. 3). The complete assembly is inserted through the nostril and once it is in place the air is withdrawn and the introducer removed. The airway itself has a flat rather than bevelled end. The airway is supplied in a sterile package and is disposable.

The clinical use of this new airway has been investigated and a comparison made with a standard red rubber airway.

MATERIALS AND METHODS

The study, which was approved by the local Ethics Committee, was carried out in patients aged 16–80 yr undergoing surgery under general anaesthesia. Patients were excluded if they had undergone nasal surgery at any time, had a history of nasal polyps, vasomotor rhinitis or a deviated nasal septum. Also excluded were patients with bleeding diatheses and those receiving medications affecting blood clotting. Anaesthesia was induced in all patients with sodium thiopentone and maintained with nitrous oxide and either halothane or enflurane in oxygen administered by face mask. Respiration was spontaneous throughout the study.

When a surgical plane of anaesthesia had been achieved, the patient was randomized to receive either a Linder or a red rubber airway (Leyland). Because external assessment may give little indication of the size of nasal passages, all female patients received a 7.0-mm tube and all males an 8.0-mm tube. No topical vasoconstrictor was used before airway insertion. The tube was lubricated (KY jelly) and the first attempt at insertion made through the right nostril. The tube was inserted over a period of 8–10 s, but if it would not pass with firm pressure, the other nostril was tried in the same manner. If the tube would not pass through either nostril, the patient was withdrawn from the study. All the airways were inserted by one of the authors (W.J.G. or A.C.P.). Systolic arterial pressure was measured immediately before tube placement and 60 s later. After the second measurement of arterial pressure, the degree of bleeding was determined by careful inspection of the pharynx using a laryngoscope at

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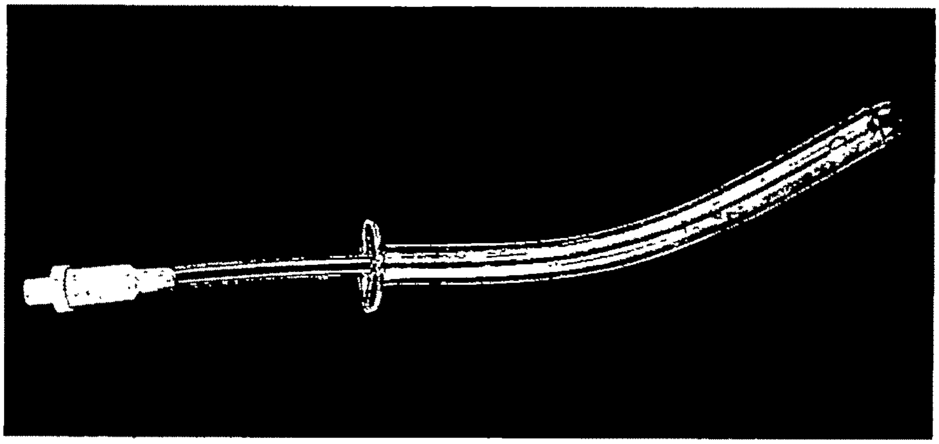

FIG. 1. The Linder Airway.

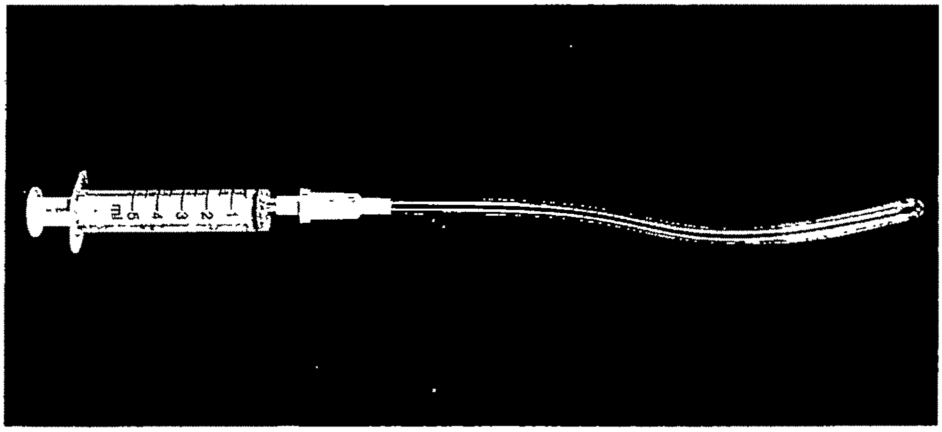

FIG. 2. The introducer.

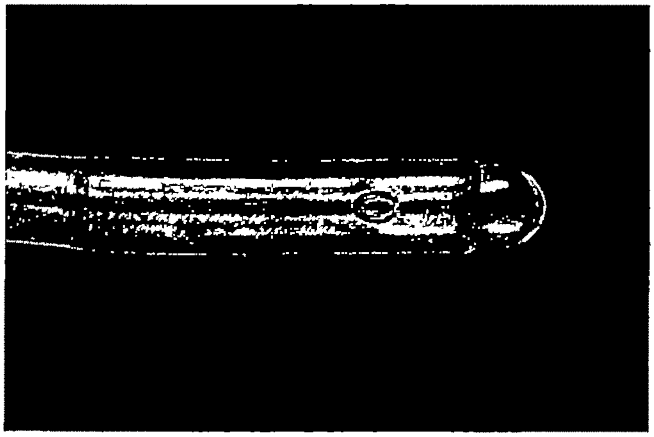

FIG. 3. The tip of the Linder Airway ready for insertion.

1, 3 and 5 min. Bleeding was graded at each time point as follows: A = no bleeding; B = blood-streaked secretions; C = small amount of free blood in pharynx; D = excessive free blood requiring suctioning to protect the airway.

The position of the distal end of the airway was noted at laryngoscopy and recorded as being short (not visible beyond the free border of the soft palate), long (within 0.5 cm of the epiglottis or more distal) or correct (in between the two previous positions).

All assessments were made with the flange of the airway touching the external nares.

Statistical analysis was by Chi-squared analysis for non-parametric data or Student's *t* tests, where applicable. A P value of less than 0.05 was regarded as significant.

RESULTS

We studied 85 patients in order to obtain successful tube insertion in 40 patients (20 male and 20 female) in each group. The means (SD) for age and weight in each group were comparable: Linder 46 (15) yr and 70 (13) kg; red rubber 47 (19) yr and 67 (13) kg.

Details of the length of the airways are given in table I. The Linder tube was more frequently of the correct length than the red rubber airway ($P < 0.001$). The red rubber tubes were frequently too long in both male and female patients. The 7.0-mm Linder tube was short in five female patients.

The incidence of bleeding is shown in table II. If bleeding occurred, it was always maximal at 3 min and this is the only time point detailed. The incidence of bleeding of all grades was12.5 % with the Linder and 27.5 % with the red rubber airway ($P > 0.05$). The incidence of free blood in the pharynx (grades C and D combined) was 7.5 % with the Linder and 20 % with the red rubber airway ($P > 0.10$). Severe haemorrhage (grade D) was seen only with the red rubber tube (two patients—5 %). These differences were not significantly different. The incidence of bleeding according to the sex of the patient is shown in table III.

There was no difference between groups in systolic arterial pressure before or after tube placement ($P > 0.20$) (table IV).

No difficulties were experienced on the introduction of the Linder tube or in the withdrawal of air from the balloon or of the introducer from the tube after placement. The length of the Linder airway was 13 cm and 15 cm for the 7.0-mm and 8.0-mm tubes, respectively. Both sizes of red rubber (Leyland) tubes were 17.5 cm long.

Of the five patients in whom an airway could not be passed through either nostril, three were in the red rubber and two in the Linder groups.

TABLE I. *Length of airway*

	Number of patients (M/F)	
Length of airway	Linder	Red Rubber
Correct	19M/15F	3M/6F
Long	1M	17M/14F
Short	5F	0

TABLE II. *Severity of bleeding*

	Number of patients	
Severity of bleeding	Linder	Red Rubber
A (no bleeding)	35	29
B (blood-streaked secretions)	2	3
C (free blood)	3	6
D (severe haemorrhage)	0	2

TABLE III. *Incidence of bleeding according to sex of patient*

	Number of patients (M/F)	
	Linder	Red Rubber
Bleeding	2M/3F	7M/4F
No bleeding	18M/17F	13M/16F

TABLE IV. *Systolic arterial pressure (mean (SD))*

	Systolic arterial pressure (mm Hg)	
	Linder	Red Rubber
Before insertion of airway	114 (19)	111 (19)
60 s after insertion	118 (21)	117 (18)

DISCUSSION

The passage of a nasopharyngeal airway is sometimes essential to prevent severe respiratory obstruction. An oropharyngeal airway may be impossible to insert during light planes of anaesthesia or in patients with anatomical abnormalities or pathology which limit mouth opening. The Linder tube was found to be more commonly of the correct length. However, the small number of patients in whom the airway was judged too short were all female. This probably reflects the empirical choice of the 7.0-mm airway, which is slightly shorter than the 8.0-mm tube, for all female patients. The airway functioned satisfactorily in these patients, but the anatomical airway may have already been fully patent in these study patients. The red rubber tubes were frequently too long and the tip could be seen—on a few occasions—lying in the oesophagus when the flange was at the external nares, so producing marked respiratory obstruction at times.

There are many reports which describe the possible hazards of passing a tube through the nasal passage, including haemorrhage, which may be so severe that the lumen of the tube becomes occluded with blood clot [1], submucosal passage of the tube [2, 3] and even the displacement of a nasal polyp [4]. However, most of these cases have appeared in the correspondence columns and the incidence of complications, including bleeding, remains unknown. Some authors have referred to the sharp bevel [5] and rigid material with which anaesthetic tubes are made [6] as the likely causes of mucosal damage. The Linder airway is made of soft plastic, has a Bubble-Tipped introducer which provides a smooth rounded tip for insertion and the airway itself has no bevel. A lower incidence of bleeding might be expected because of the softness of the plastic, the absence of bevel or the presence of the introducer.

We have shown, in a series of 80 patients, that the incidence of bleeding of all grades was 12.5% with the Linder airway and 27.5% with the red rubber. Severe haemorrhage occurred only in the red rubber group, with an incidence of 5%. However, the difference between groups was not statistically significant. Sub-mucosal placement of the tube was not seen in either group, but would not be expected to occur with the Linder tube because of the rounded profile of the distal end of the introducer. Absolute values of systolic arterial pressure, which might be considered to be an aetiological factor affecting the degree of bleeding, were not different between the groups. We did not apply a topical vasoconstrictor before tube placement in order to mimic the usual clinical situation in which a nasopharyngeal airway is used to overcome upper airway obstruction.

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CORRESPONDENCE

RE-EXPANSION PULMONARY OEDEMA: SLOW DECOMPRESSION?

Sir,—Re-expansion pulmonary oedema is a recognized and potentially lethal complication of the treatment of a pneumothorax by the rapid intercostal drainage of air. We would like to report a patient in whom recollapse of the lung following re-expansion pulmonary oedema may have prevented such an outcome.

A 23-yr-old man presented with chronic relapsing pancreatitis. A Whipple's pancreatico–duodenectomy was performed. The patient made a good recovery. Cannulation of the right subclavian vein by the infraclavicular approach was made and i.v. feeding was commenced. A chest radiograph demonstrated the tip of the catheter to be situated in the right superior vena cava and both lungs were expanded. However, on the 4th day of feeding, physical signs and a chest radiograph confirmed the presence of a right-sided pneumothorax.

Under local anaesthesia a Mallecot drain was inserted anteriorly to the right second intercostal space. When air was released it was observed to be under pressure. The catheter was connected to an underwater seal drain. Immediately the patient had a bout of non-productive coughing and became distressed, dyspnoeic and tachypnoeic, with central cyanosis. Examination revealed pale, clammy skin, a tachycardia of 130 beat min^{-1} and an arterial pressure of 140/80 mm Hg. Inspiratory crepitations were heard over the whole of the right lung field. A provisional diagnosis of re-expansion pulmonary oedema was made.

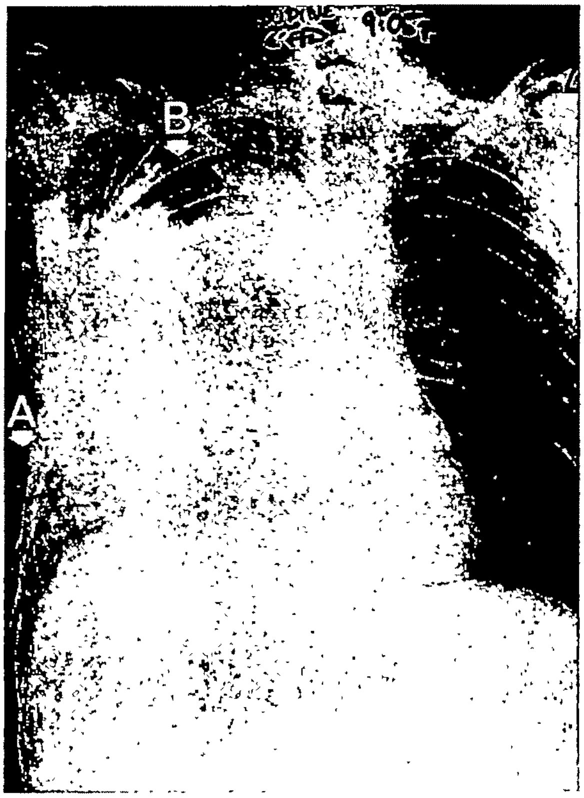

FIG. 1. Chest radiograph: A = Mallecot drain; B = central venous feeding line.

The patient was given 100% oxygen, frusemide 40 mg and hydrocortisone hemisuccinate 100 mg i.v. Radiography confirmed that the right lung was almost fully expanded, but with the appearance of pulmonary oedema (fig 1.). The patient's arterial blood-gas tensions ($FI_{O_2} = 1.0$) after re-expansion showed pH 7.53, standard bicarbonate 28.4 mmol $litre^{-1}$, base excess +5, Pa_{CO_2} 4.7 and Pa_{O_2} 4.7 kPa.

During transfer of the patient to the Intensive Care Unit, air accidently re-entered the right pleural cavity. Immediately, the patient's condition improved. Dyspnoea decreased, although air entry to the right lung decreased. The arterial blood-gas tensions were pH 7.54, standard bicarbonate 31.5 mmol $litre^{-1}$, base excess +8.5, Pa_{CO_2} 4.74 and Pa_{O_2} 10.2 kPa. Radiography showed re-collapse of the right lung. The patient's condition improved over the next 2 days as the right lung was allowed to expand slowly. Serial radiographs (over the next 5 days) showed that the pulmonary infiltration was resolving. Thereafter, postoperative recovery was uneventful and the patient was later discharged from hospital.

Re-expansion pulmonary oedema as a complication of the treatment of spontaneous pneumothorax has been described often [1–5]. Various factors appear to be implicated in the pathogenesis of the oedema. Lung collapse for three or more days [2], large pneumothoraces [3] alterations in surfactant concentration [1, 3, 4, 6] and the rapidity with which air is removed from the pleural cavity [2, 5], may be predetermining factors. Pulmonary capillary endothelial cells suffer anoxic damage during lung collapse [1]. When the pulmonary circulation is restored by expansion of the collapsed lung, the capillaries become excessively permeable to protein and fluid [7]. Management of re-expansion pulmonary oedema by slow re-expansion of the affected hemithorax does not always bring about improvement of the patient's condition [8]. However, the use of formal chest drainage and the sudden expansion of the lung in this patient was followed by pulmonary oedema. Since diuretics and increased FI_{O_2} did not improve the patient's condition, it may be reasonable to suggest that, when all else fails, re-collapse of the lung be attempted when re-expansion pulmonary oedema occurs. Later, the lung is allowed to re-expand slowly. Although the improvement in our patient's condition may have been coincidental with the re-collapse of the lung, we are unable to explain fully such a change.

A search of the literature has not revealed any similar cases. We would be pleased to hear from any of your readers who may be able to offer an explanation, or who may have had a similar experience.

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S. M. MOSTAFA
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EXTRADURAL TEST DOSES IN LABOUR

Sir,—The extradural administration of local anaesthetic agents is undertaken frequently in labouring mothers and various techniques, using test doses of local anaesthetic, are recommended to confirm that the catheter has not passed into the subarachnoid space before the full dose of local anaesthetic is given.

Test doses are usually assessed by detecting alterations in maternal arterial pressure, or the loss of motor power in the legs [1]. However, a confirmatory sign that is useful in labouring mothers is to wait for 5 min after the administration of the test dose and to observe the mother during the following contraction. If the pain from the contraction has not altered, it is unlikely that the drug has been deposited in the subarachnoid space. This sign should not be relied on alone as assessment of a test dose but, taken in combination with other methods, it can be very useful. Obviously, it cannot detect intravascular placement of the catheter.

To demonstrate the validity of the sign, it is sufficient to perform a subarachnoid anaesthetic for an operative delivery in a labouring mother and to note how quickly contractions change in nature.

Where top ups are administered by midwives, the sign could form a useful basis for them to assess test doses—a subject that is controversial [1].

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CONTINUOUS PUMP INFUSIONS FOR EXTRADURAL ANALGESIA DURING LABOUR

Sir,—The use of pump infusions for continuous extradural analgesia during labour is gaining in popularity. Several excellent articles have outlined the basic pharmacological principles and clinical guidelines of the technique [1–3]. I would like to point out, however, that patient studies generally follow a rigid regimen, whereas clinical work should be more flexible. For example, Abboud and colleagues [2] used 0.125% bupivacaine 14 ml h^{-1} alone, while Li, Rees and Rosen [3] used 10 ml h^{-1} and 8–10 ml "top-ups" of 0.125% bupivacaine if analgesia was inadequate. Both induced excellent analgesia. However, Li, Rees and Rosen [3] had an exceptionally (and to me unacceptably) high incidence of muscle weakness, with almost 80% able to flex the ankle only or nothing at all. Such an incidence of muscle weakness is unavoidable if one uses a fixed regimen as in the above studies, but is almost entirely avoidable if a flexible schedule, suited individually to each patient, is used. Our clinical guidelines for infusion pump extradurals are as follows:

(1) Establish a good block at the onset. The pump infusion will not make up for a poor extradural.

(2) Patients vary. Start with rates of 10–14 ml h^{-1} (if using 0.125% bupivacaine) and vary the rate to suit patient response. One patient (my wife) had excellent analgesia with minimal motor block with 30(!) ml h^{-1}.

(3) If motor block is significant, stop the infusion until motor power returns, then restart the infusion.

(4) If pain returns, add a reasonable top-up then continue the infusion.

(5) Be flexible. Only journal articles have to follow a rigid regimen!

With these guidelines we can provide excellent analgesia with minimal motor weakness. As already stated in this forum [4], fixed regimens do not satisfy all clinicians. They also do not satisfy all patients.

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CONTINUOUS FLOW VENTILATORS IN THE ICU

Sir,—We were delighted to read the paper by Mecklenburgh and colleagues [1], which is of great clinical interest to anaesthetists in intensive care units. The authors have shown that the increased work of breathing caused by the higher inspiratory resistance of the IMV circuit of the Kontron 3100 ventilator delayed the weaning of the patient from the ventilator. We would like to point out that the use of ventilators, like the Bird IMV, which are capable of delivering continuous flow in the IMV mode, might be more advantageous in the clinical circumstances described by the authors.

The IMV Bird is fitted with a demand CPAP system which allows the installation of an automatic baseline compensator which, among many others functions, reduces the fluctuations in the baseline pressures observed whenever inspiratory demand exceeds inspiratory flow. This, therefore, significantly reduces the work of breathing. This system is capable of giving inspiratory flow that is proportional to the inspiratory effort without altering the baseline pressures. Further, the Bird CPAP system was devised to reduce the work of breathing during the IMV mode, especially in the presence of PEEP. Most ventilatory devices provide a regulated positive end-expiratory pressure. However, during IMV procedures with PEEP, the patient may have to create substantial pressure gradients to entrain gases from the breathing circuit. This may significantly increase the work of breathing, with resultant increase in oxygen consumption and carbon dioxide production—as might have happened in the case described by the authors. We do not know if the authors were using PEEP during weaning, which might have contributed to the difficulty in weaning. When all adjustments are made in the IMV mode in the Bird IMV system (including nebulization), by an additional flow, there could be a continuous flow in the breathing circuit which might reduce the inspiratory resistance and, hence, work of breathing. The resistance of the humidifier may not be important in these circumstances.

Figure 2 of Mecklenburgh and colleagues shows an interesting finding. The slopes of A, B and C were similar, but that of D (alternate IMV) was less steep at higher flows compared with those of the ventilator circuits. Although the resistance of the ventilator alone (C) at lower flow rates was close to that of the IMV circuit, at a higher flow rates the difference between them appears to be substantial. This might suggest that the alternate IMV system was capable of delivering the higher flows required at higher inspiratory efforts more easily than the Kontron 3100 ventilator system used (inspiratory demand is better met by the inspiratory flow in the alternate IMV circuit than the ventilator). Therefore, the breathing characteristics of the alternate IMV system make it a more efficient circuit in the IMV mode than the ventilator itself. It would have been very interesting it see if the introduction of the humidifier to the alternate IMV system would increase the total resistance of the alternate IMV circuit by an anticipated 0.6 kPa or value less than 0.6 kPa.

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H. Moseley
S. MacCoskie
Y. Kumar
Barbados

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Sir,—In response to the specific question posed by Dr Shankar and his colleagues, we were not using PEEP during weaning. While not necessarily agreeing with all the claimed advantages of the IMV Bird, we think that it is undoubtedly true that, if PEEP is used during spontaneous ventilation, then gas must be available at an equal positive pressure during the inspiratory phase—unless the spontaneous breathing is to be assisted, or even deliberately hindered.

With regard to the last sentence of the letter: as we indicated in our paper (p. 1052, column 2) it would not be sensible to include a humidifier in the alternative IMV system (since it is readily supplied with humidified gas).

The main message of our paper was not to extol the advantages of the alternative IMV system, but to show that the work of breathing through an IMV ventilator may be unduly and unnecessarily great.

J. S. Mecklenburgh
I. P. Latto
W. W. Mapleson
Cardiff

NAUSEA, VOMITING AND FENTANYL

Sir,—In their recent report comparing domperidone, droperidol and metoclopramide for the prevention of nausea and vomiting following day cases, Madej and Simpson [1] stated that no studies evaluating the contribution of fentanyl to emesis exist. We are aware of five such studies involving day cases which implicate fentanyl.

Epstein and colleagues [2] studied patients undergoing dilatation and curettage or abortion using a technique of fentanyl or saline combined with nitrous oxide, oxygen and thiopentone. The authors concluded that fentanyl was associated with a higher incidence of nausea and vomiting for the patients undergoing abortions. No difference was seen between the two groups undergoing dilatation and curettage.

Henegan and co-workers [3] evaluated patients undergoing dental surgery with either nitrous oxide, oxygen and halothane or fentanyl, alcuronium, nitrous oxide and oxygen. A postoperative questionnaire revealed more nausea and vomiting in the fentanyl group.

Hackett and associates [4] compared fentanyl with enflurane for abortions. Both groups received nitrous oxide and oxygen. Nausea and vomiting was seen in 24% of those in the fentanyl group and 8% in the enflurane group.

Melnick, Chalasani and Lim Uy [5] compared enflurane, isoflurane and fentanyl for minor gynaecological procedures. All patients received nitrous oxide, oxygen and droperidol. The incidence of nausea and vomiting was 24% in the fentanyl group, compared with 8% in each of the other two groups.

Finally, Rising, Dodgson and Steen [6] studied patients undergoing laparoscopy. All patients received nitrous oxide, oxygen and suxamethonium. One group received fentanyl and the other isoflurane. Nausea was seen in 75% of the fentanyl group and 16% of the isoflurane group. The figures for vomiting were 35% and 15%, respectively.

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prevention of nausea and vomiting following gynaecological surgery in day cases. *British Journal of Anaesthesia* 1986; **58**: 879–883.
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Sir,—We would like to thank Dr Sosis for drawing our attention to five articles evaluating the contribution of fentanyl to postoperative emesis. The study by Rising and colleagues [1] was not published until after the submission of our paper. Two of the earlier articles [2, 3] were published in *Anesthesiology Reviews*. This journal is not indexed in the *Cumulated Index Medicus* and these articles were not referenced by a standard computer literature search. Our university library does not subscribe to *Anesthesiology Reviews*. Therefore, without prior awareness of the work of these authors, it was impossible to find the papers.

Neither of the remaining two papers study the influence of fentanyl alone, but compare two different anaesthetic techniques, one of which includes the use of fentanyl. In the study by Henegan and co-worker [4], a shorter period of mask ventilation [5] after suxamethonium and the use of halothane [6] may have contributed to the reduced incidence of emetic sequelae compared with the group receiving alcuronium and fentanyl. Hackett and associates [7] studied fentanyl with no volatile agent compared with enflurane and no opiate, so one cannot specify which agent is effecting the incidence of nausea and vomiting.

Thus there is evidence that techniques using fentanyl have a higher incidence of emetic sequelae than those using halothane, enflurane or isoflurane. Part of the difference may be the result of an antiemetic effect of the volatile agents. The emetic effect of fentanyl alone may not be significant in patients having dilatation and curettage [2].

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K. H. SIMPSON
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INTERMITTENT WOUND PERFUSION

Sir,—We were interested in the paper by Levack and colleagues [1] indicating that, after upper abdominal surgery, intermittent wound perfusion with 0.5% bupivacaine 10 ml produced good pain relief as shown by visual analogue pain scales. Furthermore there was an associated significant reduction in requirements for opioids when compared with a group receiving physiological saline. The authors suggested that the duration of analgesia could be prolonged by the use of continuous perfusion. Our recent experience would tend to suggest otherwise.

In a double-blind trial, 80 patients undergoing cholecystectomy were randomly allocated to receive 150 ml of either 0.5% bupivacaine or physiological saline over 60 h by

TABLE I. *Visual analogue scores, (means and ranges (mm))*

	Time after operation (h)				
	12	24	36	48	60
0.9% Saline	61	54	44	42	35
(*n* = 40)	(10.96)	(4.88)	(5.90)	(5.90)	(3.78)
0.5% Bupivacaine	53	52	44	38	32
(*n* = 40)	(13.96)	(14.95)	(5.92)	(5.85)	(3.85)

continuous infusion via an indwelling catheter lying beneath the rectus sheath. Patients with inadequate pain relief were given morphine 10 mg i.m. on demand. Both groups were comparable with respect to age, physical characteristics, mode of anaesthesia and duration of surgery.

There was no significant difference in the severity of postoperative pain between the two groups (table I).

Mean morphine requirement was 60 mg (range 15–100 mg) in the saline group, compared with 52 mg (range 10–100 mg) in the bupivacaine group (ns). These observations would suggest that, after upper abdominal surgery, continuous wound perfusion with bupivacaine may not provide better analgesia than perfusion with physiological saline.

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R. J. CUSCHIERI
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REFERENCE

1. Levack ID, Holmes JD, Robertson GS. Abdominal wound perfusion for the relief of postoperative pain. *British Journal of Anaesthesia* 1986; 58; 615–619.

Sir,—Messrs Gibbs and Cuschieri have made some interesting observations on a method of pain relief, essentially surgical in nature, and variously reported on by surgeons spanning the past 50 years.

Although not stated, their series of 80 cholecystectomy patients presumably had subcostal incisions, and there is almost full scale deflection in the range of visual analogue scores (VAS), in keeping with the notoriety of subjective methods of pain assessment. It is encouraging that, similar to our findings, they showed that saline could not be differentiated from bupivacaine by the VAS index; also, predictably, morphine requirements were similar in both groups. It is not clear how their lower limit of morphine in the saline group is 15 mg when the drug had been prescribed as 10 mg i.m. on demand.

We demonstrated improvement in forced vital capacity (FVC) associated with intermittent bupivacaine but not with saline, and whether continuous perfusion maintains this improvement has yet to be answered; it may promote more effective coughing. The technique deserves further scrutiny involving measurements in the resting chest, in particular the more inaccessible indices of functional residual capacity and expiratory reserve volume, because they may reflect a ventilatory defect associated with postoperative hypoxaemia.

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BLOOD TRANSFUSIONS AND COLORECTAL CANCER

Sir,—While none could disagree with Professor Hunter [1] that anaesthetists make a substantial contribution to the care of patients undergoing surgery for colorectal cancer by the use of skilful manoeuvres to reduce the need for blood transfusion, it would be premature for anaesthetists to feel that they had adversely affected the prognosis of their patients by administering blood. Interest in the possible influence of blood transfusion on tumour behaviour stems, first, from renal transplantation studies which, since 1973, have shown repeatedly that pre-transplant transfusion significantly reduces allograft loss from acute rejection and, second, from the fact that some tumours in humans and experimental animals are influenced by some immune responses of their hosts. It is important to note, however, that transfusion of cancer patients does not parallel transfusion practices in clinical renal transplantation: patients with cancer receive blood at the time of cytoreductive therapy, presumably long after the development of a malignant growth which itself may be associated with impairment of immune responses to antigenic stimuli [2]; potential renal transplant recipients are transfused intermittently, according to procedure, before receiving the antigenic stimulus of an allograft and intensive chemotherapeutic immunosuppression [3]. Thus conclusions drawn from studies of blood transfusion in clinical transplantation may not necessarily apply to patients with malignant disease.

There is little evidence at present to suggest a causal relationship between blood transfusion and early recurrence of surgically-treated colorectal cancer. Critical analysis of the three retrospective studies quoted by Professor Hunter shows that the presented data fail to substantiate the claim that transfusion benefits tumour growth by immunological mechanisms. Burrows and Tartter [4] (1982), Blumberg, Agarwal and Chueng [5] (1985) and Foster and co-workers [6] reported on 122, 146 and 197 patients, respectively, with primary adenocarcinoma of the colon or rectum and found statistically significant assocations between the use of blood transfusions and early cancer recurrence or cancer-related deaths. However, several important variables were omitted from these studies, including the nature, extent and duration of the surgical procedures, data regarding the number and distribution of rectal as opposed to colonic cancers amongst the transfused and non-transfused groups (rectal cancers having a worse prognosis than colonic cancers) and, perhaps most importantly, the indications for transfusion. Other problems are evident also. In Blumberg's study "patients who had not received transfusions were less likely to have received chemotherapy or irradiation or both than those who had had transfusions ($P < 0.05$)", suggesting that the transfused group contained a significantly greater number of patients in whom it was believed that surgery alone had not been curative. Foster and co-workers [6] failed to find a transfusion effect in patients with rectal cancer or advanced disease, and found that the transfused group differed significantly from the non-transfused in age and preponderance of right-sided colon cancers. The transfused patients had significantly lower haemoglobin concentrations at admission, which suggests that they had more bleeding from their tumours before surgery. Curiously, surface ulceration, which leads to bleeding from intestinal tumours, is a poor prognostic feature of malignant melanoma, the surgical treatment of which rarely requires transfusion. The major problem with the studies quoted by Professor Hunter is that the indications for transfusion were not identified, and as the studies were not randomized the two subject groups are not strictly comparable.

A smaller retrospective study of 87 patients undergoing surgery for potentially curable cancer of the colon and rectum at the Royal Melbourne Hospital showed a non-significant increase in the rate of recurrence in transfused patients [7]. However, the incidence of recurrence was significantly greater in those patients who received blood during surgery than in those who were transfused either before or after surgery (15 of 29 (52 %) compared with 4 of 24 (16 %) $\chi^2 = 7.01$, d.f. = 1, $P < 0.01$) or who were not transfused at all (15 of 29 (52 %) compared with 9 of 34 (26 %); $\chi^2 = 4.23$, d.f. = 1, $P < 0.05$). This finding suggests strongly that the need for transfusion during surgery had a greater influence on cancer recurrence than receipt of a transfusion *per se*. The timing of transfusion in relationship to surgery was not considered in other studies [5, 6], but is obviously a very important variable.

While there is increasing evidence from animal studies that allogenic blood transfusion can influence tumour growth [8–10] and that this tumour promoting effect is T-lymphocyte dependent [11], a causal relationship between transfusion and cancer recurrence has yet to be established in man. Even if such an association was identified by prospective studies, it might not be necessary to implicate immunological mechanisms—blood transfusion could be simply identifying tumours which were particularly difficult to resect and were associated with more handling, greater spillage and dissemination of tumour cells, longer operations and greater blood loss.

Until properly conducted prospective studies are performed, avoidance of transfusion cannot be justified purely on the basis of hoping to prevent early cancer recurrence. If the intriguing studies mentioned by Professor Hunter serve only to stimulate clinicians to re-evaluate the indications for transfusion, they will have made a valuable contribution to patient care.

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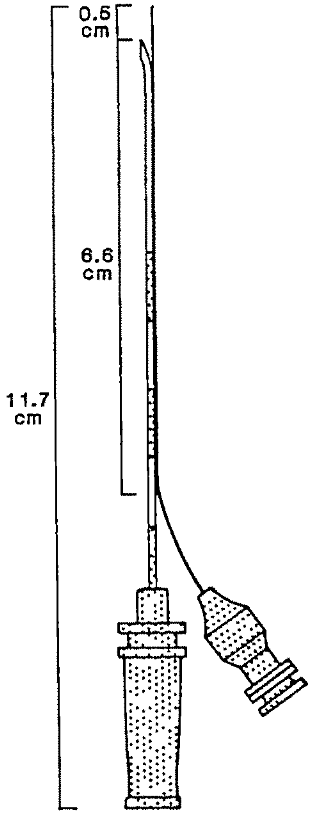

FIG. 1. The combined spinal–extradural technique.

COMBINED SPINAL–EXTRADURAL ANAESTHESIA FOR PROSTATECTOMY

Sir,—We are referring to the article written by Millar, Jago and Fawcett [1]: Spinal analgesia for transurethral prostatectomy: comparison of plain bupivacaine and hyperbaric lignocaine. These authors found that 3.9% of patients in the bupivacaine group needed general anaesthesia because the block was inadequate, and a further 5.8% required supplementation with nitrous oxide or fentanyl. In the lignocaine group there was 8.3% failures and 10.4% required additional systemic analgesia.

We believe that, since the letter of Coates [2] on the combination of subarachnoid and extradural techniques, there is no justification for a general anaesthetic following a failed spinal block. Instead, there has to be a policy of a combined spinal–extradural approach to such operations so that it is possible to assure the patient that under no circumstance will general anaesthesia be given at the operation.

This approach also is valuable as a postoperative method of analgesia through the extradural catheter. Our method is a little different from the methods described previously [3–5]. First, we insert the extradural needle to the extradural space. Then we insert along side it (but not inside it as others have done) the spinal needle (fig. 1). After obtaining spinal fluid we inject the anaesthetic solution, and then we withdraw the spinal needle, and insert the extradural catheter through the extradural needle. With this approach we facilitate the insertion of the spinal needle, and do not need to supplement the spinal anaesthesia with general anaesthesia in failed spinals. Instead, we supplement it with top-up extradural injections, and we administer extradural methadone to provide postoperative analgesia.

J. Eldor
D. Olshwang
Jerusalem

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Sir,—Thank you for the opportunity to reply to the letter from Drs Eldor and Olshwang referring to our article spinal analgesia for transurethral prostatectomy.

There are two separate issues here. First, our study was undertaken to establish if plain bupivacaine is a suitable agent for spinal analgesia for transurethral prostatectomy; at the time heavy cinchocaine had been withdrawn and heavy bupivacaine was not yet available. For the purpose of the study, a technique such as they describe would have been inappropriate as it would not have enabled us to assess the efficacy of the bupivacaine alone.

The second issue is whether a combined extradural and spinal approach with postoperative extradural methadone is the ideal technique for transurethral prostatectomy. A frequent criticism of spinal anaesthesia is the time taken to prepare the patient, particularly if the anaesthetist is single-handed. We found that, in experienced hands, the delay with spinal alone was minimal; the combined approach would take much longer. The failure rate with plain bupivacaine was small—fewer than 4% of patients required general anaesthesia, and this usually consisted of inhalation of a low concentration of enflurane to cover a block which was imperfect, rather than a total failure. Finally, the requirements for postoperative analgesia in transurethral prostatectomy are not great or prolonged. Notley and Schweizer's study [1] showed that only 5% of patients required narcotics after operation and, in our study, 18.8% of the lignocaine group and only 1.9% of the bupivacaine group required analgesia in the 6 h following operation. The risks and undesirable side effects of extradural opiates, particularly in elderly patients who may have respiratory impairment, have been well reviewed [2, 3]. Most anaesthetists would consider that these would outweigh the benefits if, as is usually the case, close postoperative supervision in a high dependency unit or equivalent is not readily available.

There is no doubt that the suggested technique would provide an excellent standard of care, given the right facilities, but it would be unnecessarily costly in time and resources, with minimal extra benefits. We would regard it as gilding the lily.

J. M. Millar
Oxford
R. H. Jago
Reading

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THE "ARM-DROP" TEST AND THE PRIMING PRINCIPLE

Sir,—The "priming" principle provides rapid onset of intubating conditions and represents an alternative to suxamethonium when circumstances contraindicate the use of this agent [1–3]. Engbaek and Viby-Mogensen [4] and others [5] have reported the unpleasant combination of wakefulness and profound muscular relaxation in patients receiving "subparalytic" doses of myoneural blocking drugs. On occasion this led to psychiatric sequelae requiring prolonged treatment.

Bar [6] described the "arm-lift" test to determine residual muscle weakness following antagonism of neuromuscular blockade. We would like to report a preliminary study which untilized the "arm-drop" test in 21 patients who received either vecuronium 0.1 mg kg^{-1} or atracurium 0.4 mg kg^{-1}, primed by either atracurium 80 μg kg^{-1} or vecuronium 20 μg kg^{-1}.

The first onset of blockade following the priming dose was detected by descent of the arm previously raised to 45°. Inability to sustain this position for 6 min post-priming was used as the end-point to proceed with induction. Intubating conditions and times were comparable to those obtained when using suxamethonium (Lawes et al., in preparation) whilst, most importantly, there was no case of recall of unpleasant weakness before induction. Failure of arm-drop forewarned against difficulty in intubation. The technique takes into account the wide range of sensitivities to neuromuscular blocking agents demonstrated by individuals and eliminates the need for an arbitrary fixed interval between priming and induction.

D. Goodrum
Bristol

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Br. J. Anaesth, (1987), **60**, 123–124

BOOK REVIEWS

Medical Assessment of the Elderly Surgical Patient. By G. Seymour. Published by Croom Helm. Pp. 305; indexed; Price £30.

This book begins with an assessment of the provision for and estimated needs of the geriatric surgical population. It concludes by summarizing and evaluating proposed preoperative risk factors, with a plea to view these as a challenge to be met by the further development and practice of a high standard of perioperative care. The intervening eight chapters consider the respiratory, cardiovascular, renal and central nervous systems, malnutrition, sepsis, thromboembolism and laboratory tests in the elderly surgical patient.

A meticulous appraisal of the literature forms the basis for a logical discussion of important issues and common problems and at the end of each chapter recommendations based on the preceding discussion are made for practical patient management. A straightforward critical approach identifies and subdivides data into proven, unproven and absent categories in the fields covered. One of the less satisfactory aspects of the book is the lack of hard facts in many areas. On occassion, notably in the section on deep venous thrombosis and pulmonary embolism, the available information is contradictory. Suggestions are made for further studies and the use of multi-variate statistical analysis, in the identification of risk factors and outcome prediction, is enthusiastically advocated.

The division and sub-division of the text into numbered sections which are itemized at the beginning of each chapter allows easy reference to specific pieces of information, much of which is summarized in tabular form.

The author, who is a geriatrician, expresses the opinion that the assessment and management of elderly patients' medical problems in the perioperative period remains, in general, the province of the anaesthetist and surgeon. Although rather expensive for a relatively slim volume, this book provides a rational framework for decision-making in this important area and, as such, should be obligatory reading for trainees in anaesthesia. The comprehensive update on the many issues affecting perioperative morbidity and mortality will also make it of interest to their senior colleagues.

T. A. Goudie

Evoked Potential Monitoring in the Operating Room, 1st Edn. By M. Nuwer. Published by Raven Press, New York, Pp. 246; indexed; illustrated.

The preface states that this book is meant to serve as a resource for anaesthetists, surgeons and operating room nurses, to understand better the basic principles and methodologies of the growing branch of clinical neurophysiology. It is divided into seven chapters: Introduction to Evoked Potential Monitoring, Basic Electrophysiology, Spinal Cord Monitoring, Other Somatosensory Techniques, Brainstem Auditory Monitoring, Visual System Monitoring, and Basic Science Studies of Monitoring. The book has been written by a single author and, therefore, does not have much of the repetition common in multi-author texts. The references are all gathered together alphabetically at the end of the text.

The chapter on basic electrophysiology is very good. It contains details of the purported generators of evoked potentials. It describes the recording equipment, the techniques of signal processing and problems with artefact. It also provides useful information on safety and technical aids. This chapter would be useful to anyone required to make a decision about the purchase of equipment for intra-operative evoked potential monitoring.

The third chapter, on spinal cord monitoring, is extremely detailed. It is written very much from the neurophysiologist's view-point and concentrates little on the effects of anaesthetics—which occupy three pages in a chapter of over 50 pages. The next three chapters, on somatosensory evoked potential techniques, auditory evoked potential techniques and visual evoked potential techniques, provide the information necessary to establish these type of recordings in clinical practice. They also discuss the circumstances under which various workers have found them useful. The final chapter on basic science studies in monitoring provides much of the background to our current understanding of evoked potentials. This chapter concentrates mainly on animal research work. Again, much of this chapter is about spinal evoked potential monitoring.

This book is written in a somewhat dry and mechanical style, which does not make for easy reading. Although designed for the anaesthetist, it is written very much from the view-point of the neurophysiologist. The chapter on electrophysiology, however, is of major use to the anaesthetist who wishes to involve himself with evoked potential monitoring. The book is very American in its approach and concerns itself with a technology that is widely available in the U.S.A., but has limited availability in this country. The emphasis of this book is very much on spinal cord monitoring; other modalities receive somewhat less attention than they possibly deserve. This is a book that can be recommended to the clinician who requires detailed information about evoked potential monitoring.

P. S. Sebel

Cardiac Anesthesia, Second Edition. Edited by J. A. Kaplan. Published (1987) by Grune and Stratton, Orlando. Pp. 1122; illustrated; indexed. Price $124.5, £92.50.

The second edition of this book brings together, under one title, two of the editor's previous works, *Cardiac Anesthesia* and *Cardiovascular Pharmacology*. Since these works were originally published in 1979 and 1983 respectively, the field of cardiac anaesthesia has continued to grow at a rapid pace, a fact reflected well in the second edition which has been updated and expanded extensively. Although aimed principally at the cardiac anaesthetist, this book will also be of value to other specialists involved in cardiac surgery and all anaesthetists who deal regularly with patients suffering from cardiac disease coming to surgery for other reasons.

The text is allocated to two volumes covering all aspects of cardiac anaesthesia. Volume 1, with 14 chapters, is in three sections. The first section deals with the pharmacology of the inhalation and i.v. anaesthetic agents, opioids and the newer neuromuscular blocking drugs. Throughout, the pharmacodynamics and pharmacokinetics of these agents are considered in relation to the cardiovascular system in health and disease. The second section concentrates mainly on the monitoring of the cardiovascular system and includes excellent reviews of newer techniques such as transoesophageal echocardiography and recent advances in ECG techniques. Additionally, there is a valuable chapter dealing with the monitoring of the central nervous system during cardiopulmonary bypass. The final section in the first volume is devoted to the preoperative assessment of the cardiac surgical patient and covers the treatment of hypertension, angina, arrhythmias and heart failure.

Volume 2, with 18 chapters, is also in three sections, the first of which deals with anaesthesia for all types of cardiac surgery, including cardiac transplantation. There is an excellent chapter on thoracic aortic disease and a useful section dealing with uncommon diseases and cardiac anaesthesia. The second section opens with a detailed but easily understandable account of the management of cardiopulmonary bypass and continues with a good review of current thoughts on myocardial protection. The final three chapters in this section give a detailed account of the management, both pharmacological and mechanical, of the failing circulation and includes a fascinating abstract from the 11-page consent form signed by patients about to undergo implantation of a totally artificial heart. The final section is devoted to the postoperative care of the cardiac surgical patient in terms of ventilatory management, circulatory control and nutrition. The book ends with a comprehensive and salutory review of the complications of cardiac surgery.

Despite the large number of contributions (55), the book is compiled in such a way as to avoid unnecessary repetition and conflict, a tribute to the editor. It contains hundreds of excellent illustrations and an extensive and up to date bibliography. Whilst reluctant to criticize such an excellent text, I was rather surprised to find a number of errors where tables had been labelled incorrectly and sections of text had been repeated inappropriately. These minor errors should have been detected at least at the page proof stage, and this suggests the proof reading was not undertaken as carefully as the writing.

Despite this, I would agree with the reviewer of the first edition that this is the best available text in the field and will continue to be essential reading for all cardiac anaesthetists and a source of reference for others dealing regularly with patients suffering from cardiac disease.

G. Weston

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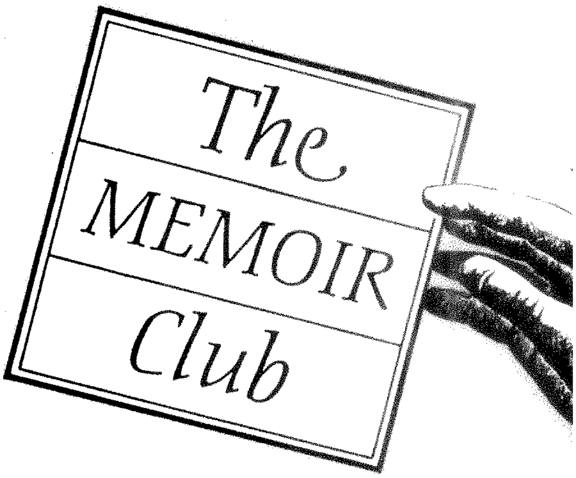

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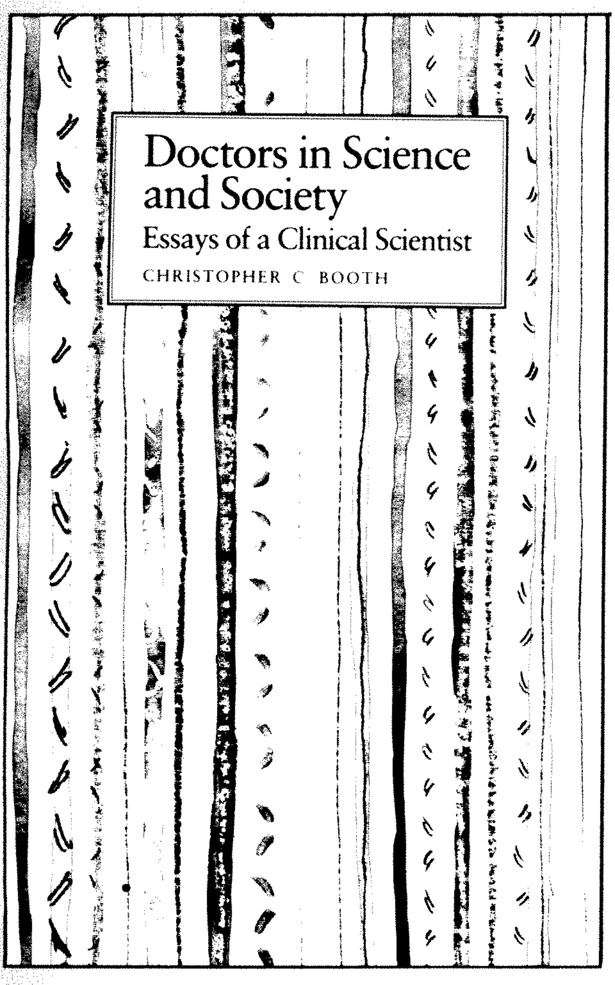

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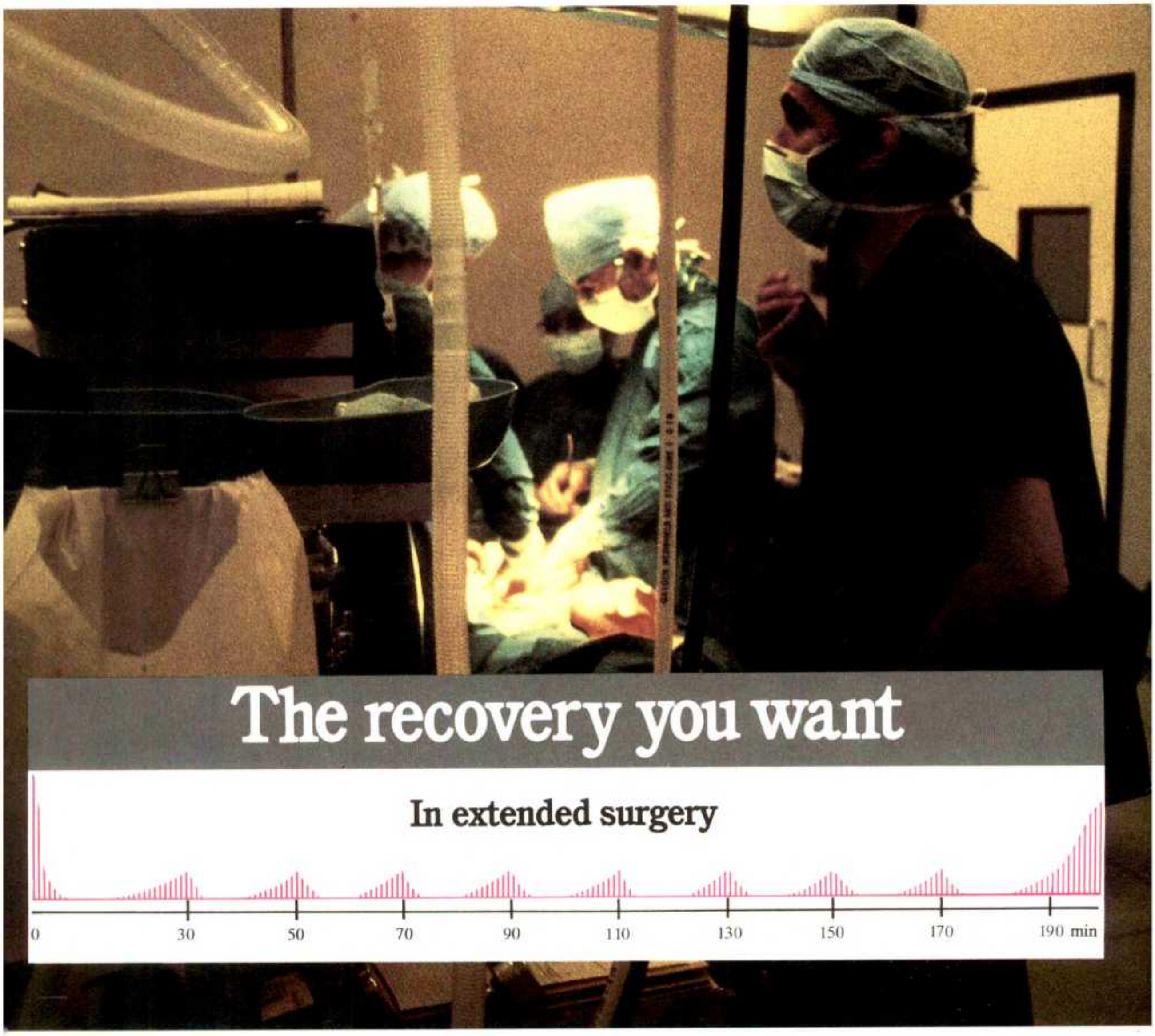

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1. Data on file, Wellcome, 1987.
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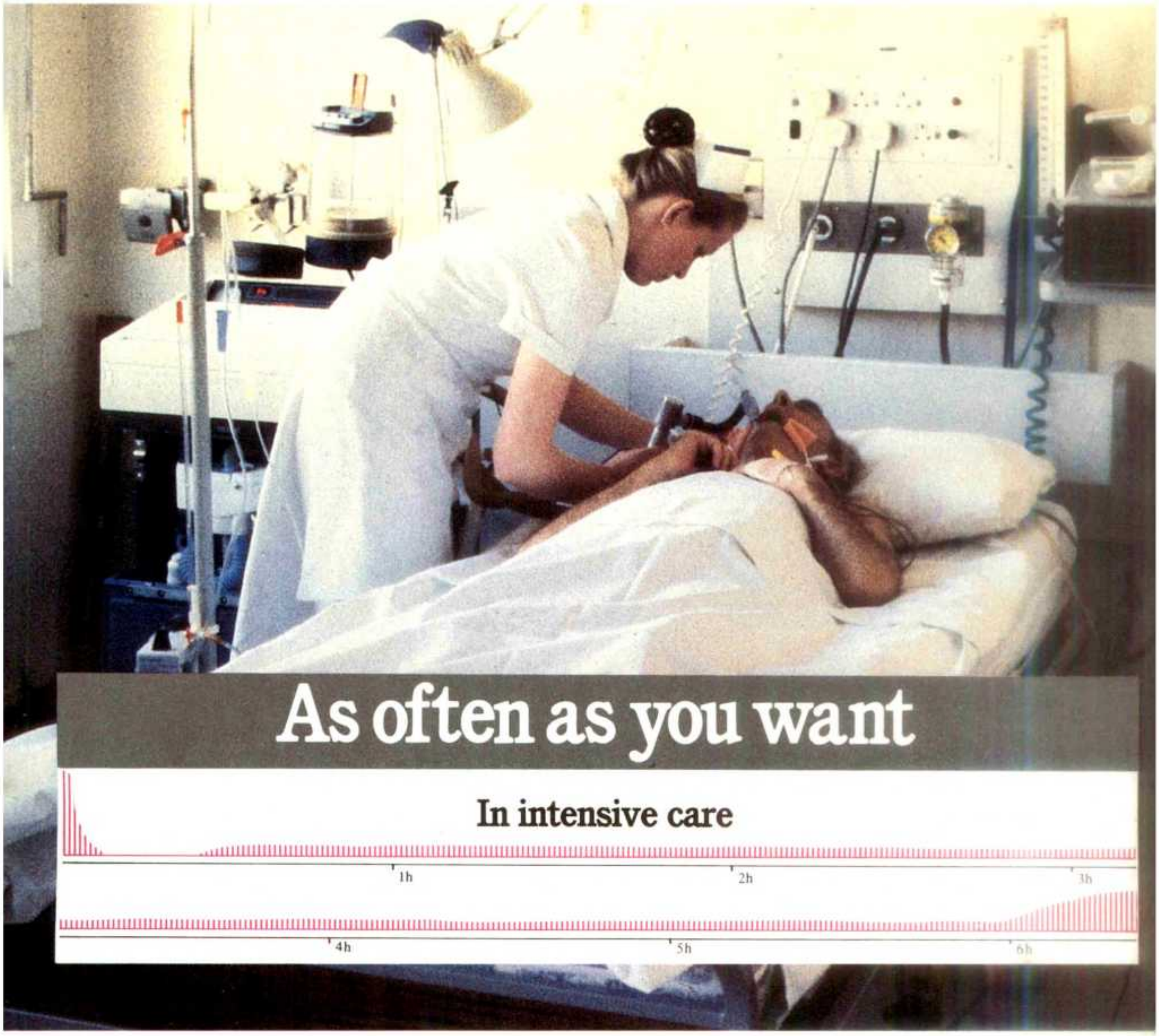

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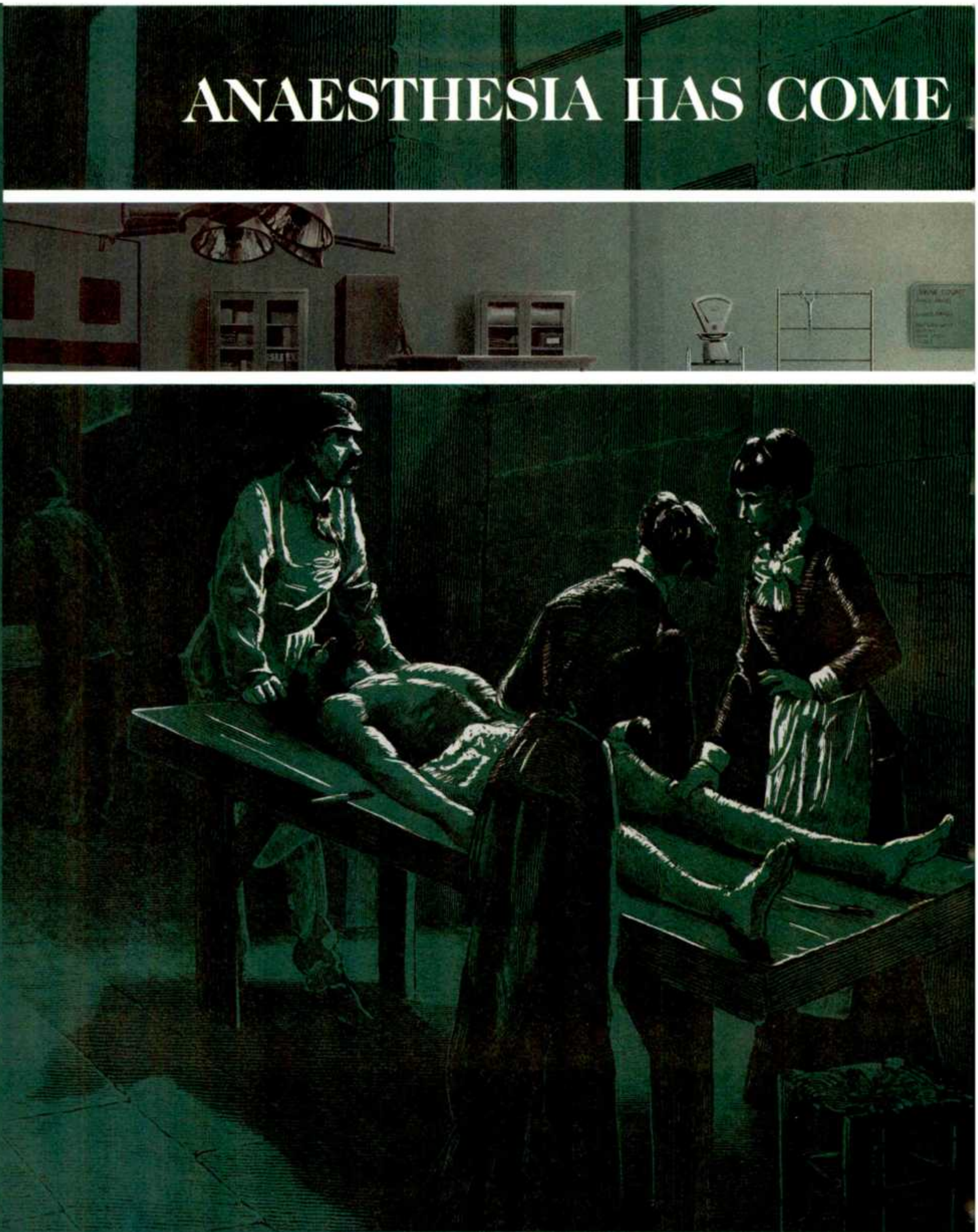

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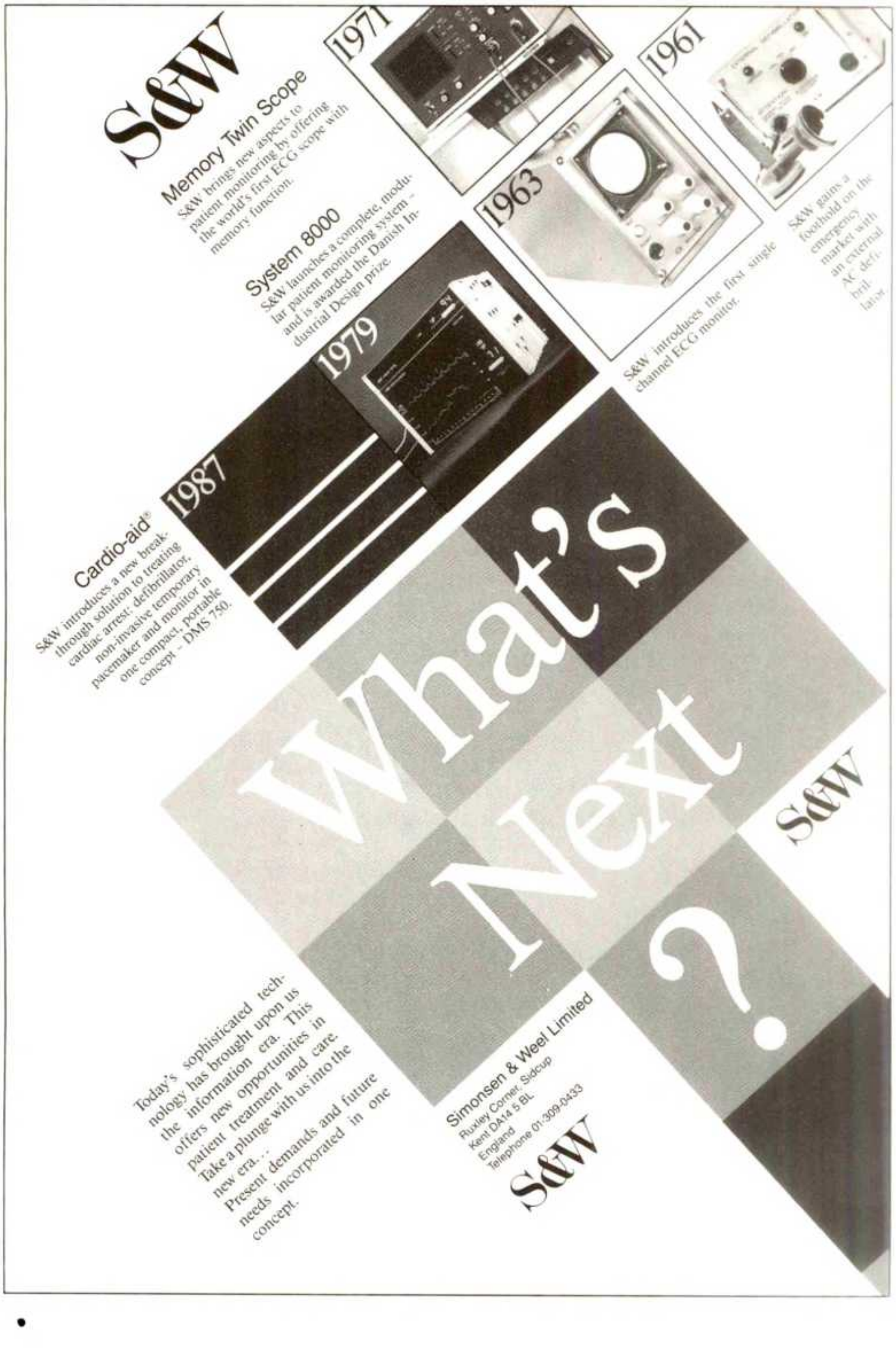

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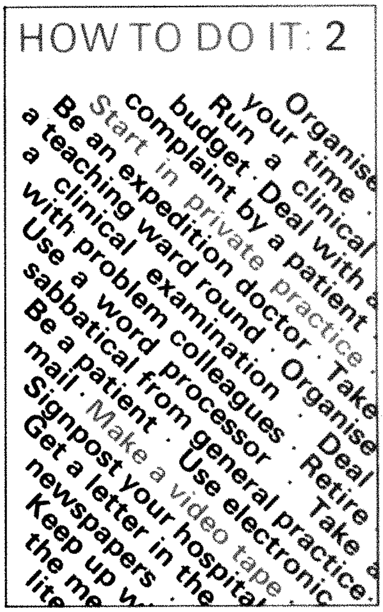

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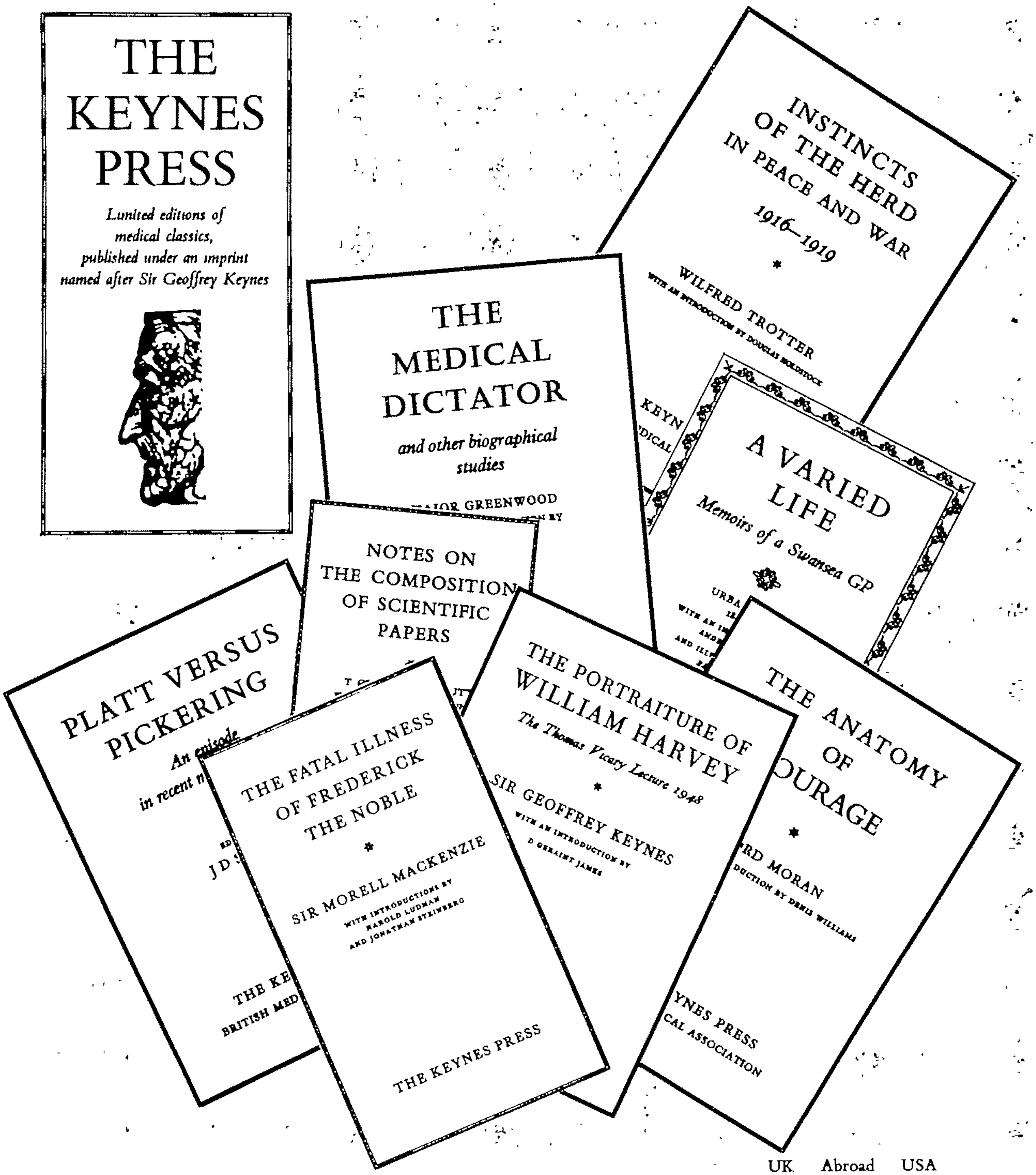

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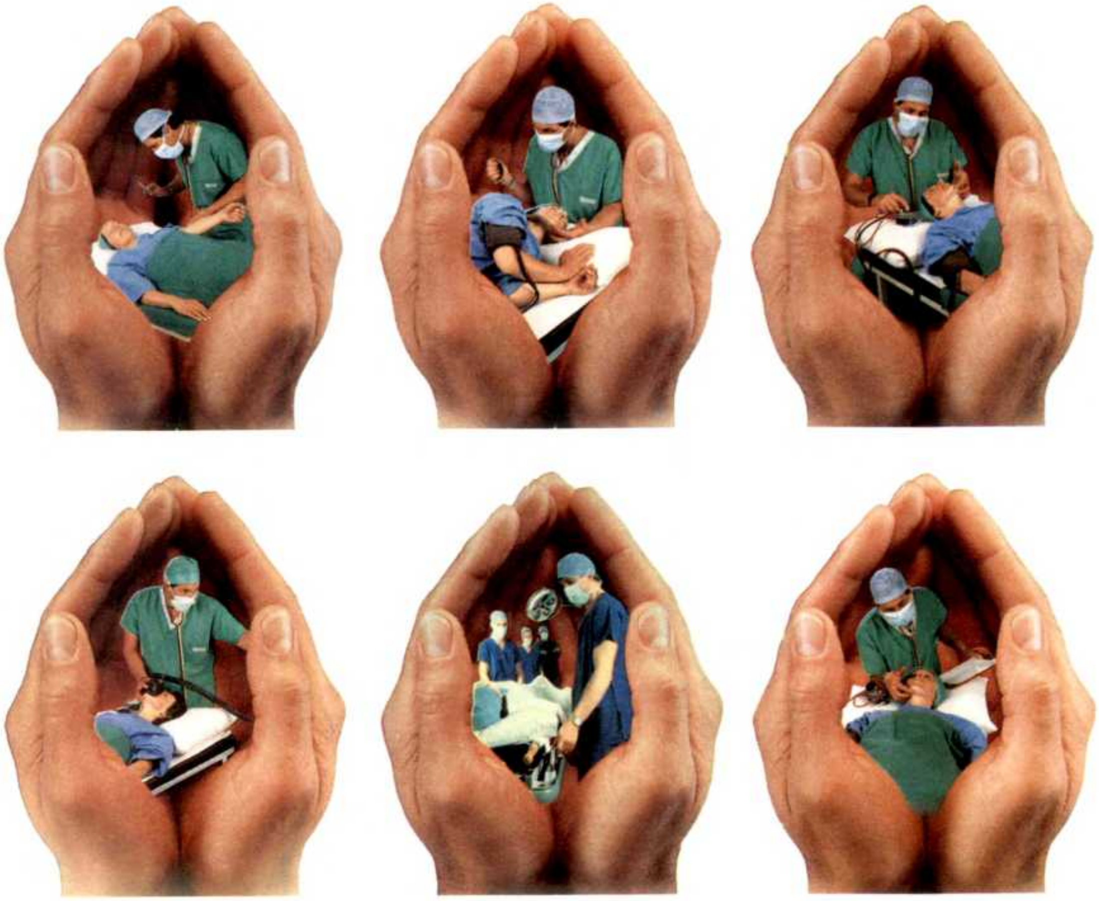

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EDITORIAL

THE RISK OF ADVERSE REACTIONS IN ANAESTHESIA

Adverse drug reactions are regarded as a serious problem in anaesthesia, as indeed they are in therapeutics in general. An international symposium, entitled The Perception, Measurement and Management of Therapeutic Risk, provided a forum for many experts in this field to bring the problem into perspective. The symposium was presented by the Trust for Education and Research in Therapeutics, in conjunction with the Drug Safety Research Trust, Southampton [1]. The majority of delegates were from the pharmaceutical industry, and most of the discussion regarded long-term oral therapy, but many points are of particular relevance to drug related adverse events in anaesthesia.

Risk Watch: *the Odds of Life*, by John Urquhart and Klaus Heilmann [2], is one of the definitive texts concerning the risks of modern day living, including exposure to medical practice and disease. Both these authors contributed to the seminar.

Professor Heilmann described the factors that are often emphasized or disregarded when assessing the degree of risk associated with therapeutic intervention. It is human nature to panic in the face of sudden unfamiliar disasters, but to accept, without concern, less dramatic events. An occasional severe reaction to a drug leads to far more concern than that generated by the enormous daily death toll on our roads. If three fully loaded 747 jumbo jets crashed every day, few people would continue to travel by air. However, this number of deaths (540000 per year) is approximately equal to the number of premature deaths in the U.S.A. caused or accelerated by smoking.

Reporting of drug related events by the media often influences the perception of risk. However, it is important to remember that the function of the media is not only to inform but also to entertain. This leads inevitably to varying degrees of sensationalism and "victim orientated reporting." This term refers to a style of reporting seen too often in the general and medical press. Let us take an example in anaesthesia by considering the following head-line concerning a new neuromuscular blocking agent: "Three patients die on exposure to Relaxium." This type of reporting does not tell us how many patients were exposed to this drug on this occasion, what other influences were acting on the patients at the time, the total number of patients ever exposed to the drug, or the benefits other patients may have gained from Relaxium. It seems that it is the view of many medical practitioners, most of the general public and all of the media reporters, that drugs should be perfect. Unfortunately, this is not yet the case. But has this attitude been responsible for the premature removal from the market of useful drugs?

At a time when medical specialties are becoming increasingly complex, dependence is placed to a large extent on the opinions of experts. In the case of adverse reactions to drugs, it is extremely common to find strongly differing expert opinions. Statements are often equivocal and conflicting. How can members of the public, both general and medical, have confidence in doctors and the pharmaceutical industry in these circumstances?

Professor Heilmann also made a plea to those responsible for the withdrawal of a drug to take full account of the consequences of their absence. The removal of any drug may result in a less effective and more dangerous replacement, but this problem may not concern the company withdrawing the drug, often in response to a campaign waged against it. How important, in arriving at this decision, is the company's desire to save its other products?

How do these factors contribute to the decision to withdraw an anaesthetic agent? It has been suggested that victim-orientated reporting, panic, conflicting expert opinions, fear of drug companies and no consideration of the consequences to patients of removal of the drug, all played a part in the removal of Althesin [3]. How many of these factors influence the debate on halothane toxicity and will they eventually be responsible for its withdrawal?

Dr Urquhart, the co-author of *Risk Watch: The Odds of Life*, stressed the importance of accurate measurement and reporting of risk levels. The risk of an adverse event is often quoted as, for example, 5 per 100000. This is equivalent to 1 per 20000, which gives instantly a clearer picture of the likelihood of harm. Dr Urquhart called for all risks to be quoted in this way and defined the population at risk, in this example the 20000, as a "unicohort". The unicohort, therefore, is the number of people at risk of a particular hazard divided by the total number of individuals who become victim to the hazard per unit time. The degree of risk is related inversely to the size of the unicohort.

An example of the usefulness of this concept is provided by the number of deaths occurring in scheduled airline flights in the U.S.A. In 1960, 499 passengers died, compared with 655 in 1977 [2]. It would seem, at first glance, that flight safety had not improved in those 17 years. However, this is an example of victim-orientated reporting and further analysis of the data reveals a different picture. The number of passengers exposed to the risk of death in these 2 years was 62 million in 1960 and 240 million in 1977. This gives unicohorts of 0.124 and 0.366 million, respectively. The unicohort immediately shows that the chances of death in flight were three times greater in 1960 than in 1977. A similar approach has been used for some time by the Adverse Drug Reactions Group of the Committee on Safety of Medicines.

Professor William Inman, Director of the Drug Safety Research Unit, discussed post-marketing surveillance. He called for the abandonment of "promotional" surveillance. This process, undertaken by the pharmaceutical company, is expensive, poorly controlled and often selective, as high risk patients are usually omitted. Therefore, the data obtained are of low credibility and often inaccessible to those outside the company. Furthermore, this method of audit may damage the efficiency of the more established monitoring systems.

Dr Geoffrey Venning gave a view of the problem, based on his considerable experience in the pharmaceutical industry. He suggested that most experts focused their attention on idiosyncratic drug reactions (type B). Dose-dependent reactions (type A) were often ignored. Type A reactions caused more deaths than type B, and as evidence for this he presented his review of the adverse drug reaction literature published in 1983 [4]. Only five of the 61 deaths reported were type B reactions, and of the 56 deaths resulting from type A reactions, 38 were probably or possibly avoidable. He suggested that the dose chosen for a new drug in phase II of its development had not been shown always to be the most appropriate, based on safety and efficacy data. He conceded, however, that volatile anaesthetic agents were an exception, as a result of the intensive monitoring performed by anaesthetists. Dr Venning's evidence invites the following question: how many reactions to anaesthetic agents reported as idiosyncratic are, in fact, type A reactions caused by inappropriate dosage?

Professor William Asscher, Chairman of the Committee on Safety of Medicines, described the established methods of detecting adverse drug reactions. Clinical trials detect adverse reactions only if they are relatively common (1 in 100). The yellow card reporting system may detect reactions as rare as 1 in 10000. No discussion was held on the role of yellow cards in anaesthesia, but this question has been reviewed previously [5].

It is our view that anaesthetists have a special duty to report on adverse drug events because of their close personal involvement in drug administration. Also, because of the nature of anaesthesia and intensive therapy, anaesthetists may be tempted to use drugs in ways which lie outwith the product licence. A doctor incurs a considerable degree of professional responsibilty in this case and is wise to record in the notes the reasons for using the drug outside its product licence. Patients should be monitored carefully during this time and observations should be noted.

This seminar, therefore, emphasized several points of relevance to anaesthesia when considering adverse drug reactions. The risk of a reaction must be defined clearly and reported in a clear and unsensational manner. Before removing a drug from the market, the consequences of its removal must be considered fully and other influences such as market forces should be ignored. Finally, the most important consideration when making decisions regarding availability of a drug should be the welfare of our patients. Responsible adverse drug reaction reporting should assist this aim.

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PLASMA GLUTATHIONE S-TRANSFERASE CONCENTRATION AS A MEASURE OF HEPATOCELLULAR INTEGRITY FOLLOWING A SINGLE GENERAL ANAESTHETIC WITH HALOTHANE, ENFLURANE OR ISOFLURANE

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SUMMARY

The plasma concentration of hepatic glutathione S-transferase (GST) was measured in matched groups of patients who received halothane, enflurane or isoflurane anaesthesia for elective minor surgery. The GST concentrations increased significantly at 3 h after anaesthesia in patients who received halothane or enflurane, but not in patients who were given isoflurane. A secondary increase in GST concentration, at 24 h, was seen in a small number of individuals who received halothane or enflurane. Abnormal GST concentrations were found in 50% of patients following halothane anaesthesia, 20% following enflurane and 11% after isoflurane. The small but significant increases in GST concentrations in patients receiving halothane or enflurane suggests an impairment of hepatocellular integrity following the administration of these anaesthetics. In contrast, isoflurane anaesthesia did not appear to be associated with this effect.

Hepatic injury has been associated with the use of volatile halogenated anaesthetic agents [1]. Halothane, a volatile anaesthetic agent still used widely in Great Britain, is the subject of renewed controversy, with acute fulminant hepatitis occurring rarely following its use. The incidence and underlying mechanisms leading to the development of "halothane hepatitis" still remain unknown, but biotransformation [2], a susceptibility factor [3], and hypersensitivity [4] have all been implicated.

With recent reports [5, 6] questioning the future of halothane in clinical anaesthesia, anaesthetists may turn to alternative anaesthetics such as the newer volatile agents, enflurane and isoflurane. However, there have also been reports of hepatic injury associated with enflurane anaesthesia [7, 8]. It has, therefore, been postulated that there is a syndrome of "enflurane hepatitis". Hepatic dysfunction after administration of isoflurane is unlikely [9].

The most widely used method of assessing drug-induced hepatocellular damage in man is the measurement of transaminase activity in plasma [10]. However, these measurements lack sensitivity and may have poor organ specificity. The measurement in plasma of the hepatic isoenzymes of glutathione S-transferase (GST) by radioimmunoassay is a sensitive and specific method for the detection of acute drug-induced hepatocellular damage. In chronic liver disease, the measurement of GST, unlike the aminotransferases, correlates well with liver histology (for a review see [11]). The physicochemical properties of GST offer certain theoretical advantages over measurements of aminotransferase in the investigation of chemically-induced hepatotoxicity. GST are relatively small enzymes (MW ~ 50000) and are present in high concentrations in hepatic

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cytosol. GST are readily and rapidly released in quantity into the circulation following hepatic damage; their short plasma half-life (< 90 min) allows early detection of hepatic damage and its resolution. Unlike the transaminases, which are located periportally, GST are primarily located in the centrilobular hepatocytes [12]. The measurement of plasma GST may, therefore, be of particular relevance in investigating halothane hepatitis, since this syndrome is generally associated with centrilobular necrosis.

We have shown that significant increases in plasma GST concentration occur 3 h after halothane anaesthesia, but not after isoflurane anaesthesia [13, 14]. This suggests that halothane, but not isoflurane, is associated with a mild, transient impairment of hepatocellular integrity. In the present study, we have investigated sequential changes in plasma GST concentration in three matched groups of patients allocated to receive anaesthesia with halothane, enflurane or isoflurane, for surgical procedures that were standard in type and duration.

PATIENTS, MATERIALS AND METHODS

Patients and samples

Only patients undergoing herniorraphy or varicose vein surgery in ASA groups I or II were included in the study. Ethical approval and informed consent were obtained. Patients with pre-existing clinical or biochemical evidence of liver disease or who had received a general anaesthetic in the previous 6 months were excluded. Patients taking regular medication likely to interfere with liver function were also excluded.

Subjects were allocated to three groups: patients in group A received halothane ($n = 30$), group B patients received isoflurane ($n = 30$) and patients in group C received enflurane ($n = 41$). No premedication was given. Anaesthesia was induced with thiopentone 4–6 mg kg^{-1} i.v., and maintained with the volatile anaesthetic agent vaporized in 33 % oxygen and 67 % nitrous oxide. Ventilation was spontaneous in all subjects. During maintenance of anaesthesia, the inhaled fresh gas concentration of halothane varied from 1.0 to 1.5 %, and those of isoflurane and enflurane from 1.0 to 3.0 %. Diamorphine was given i.v. in divided doses at induction and on recovery to a total dose of 0.07 mg kg^{-1}.

Blood samples were taken before the induction of anaesthesia and at 3, 6 and 24 h following the termination of anaesthesia. Plasma concentrations of albumin, alanine aminotransferase (ALT), bilirubin, γ-glutamyltransferase (GGT) and alkaline phosphatase (ALP) were measured in the samples obtained before anaesthesia and at 24 h following anaesthesia. Plasma from all samples was stored at −20 °C before measurement of GST.

Assay procedures

Concentrations of albumin, ALT, bilirubin, GGT and ALP were measured using a Sequential Multiple Analysis with Computer (SMAC) System II (Technicon Instruments Corporation, Basingstoke, U.K.). The concentration of GST B_1 in plasma was measured using a specific radioimmunoassay [15]. The reference range for GST B_1 is 0.7–4.0 µg litre^{-1} (derived from 135 blood donors). The inter-assay coefficient of variation for the GST B_1 RIA was less than 10 %, and the intra-assay coefficient of variation was less than 5 % over the range 2–40 µg litre^{-1}.

Statistical analysis

The Kruskal–Wallis test, for analysis of variance, was used to compare the changes in GST concentrations observed in the three groups, at 3 h following anaesthesia, in order to eliminate multiple testing errors. Changes in GST concentrations within each group were compared using the Friedman test. The Wilcoxon matched-pairs test was used to compare postoperative concentrations of GST and albumin with preoperative values in groups that showed significant changes with the Friedman test. Correlation analysis used the Spearman rank test. A four-fold table chi-squared test was used to compare the incidence of abnormal values in each group. The demographic data from each group were compared using the Kruskal–Wallis test.

RESULTS

Patients with preoperative plasma concentrations of GST, ALT, bilirubin, ALP or GGT that exceeded the upper limit of the reference range were excluded from the study. Statistical analysis of the demographic data for the remaining subjects in group A ($n = 22$), group, B ($n = 18$) and group C ($n = 30$) showed no significant differences (table I). No significant overall changes in the concentrations of bilirubin, ALT, ALP or GGT occurred as a result of anaesthesia.

Significant differences in the changes in GST concentrations following anaesthesia between the three groups were observed (Kruskal–Wallis: $P < 0.05$), and significant temporal changes in GST concentrations were evident within all three groups (Friedman; group A $P < 0.05$, group B $P < 0.01$ and group C $P < 0.0001$). In groups A and C, that is those patients receiving halothane and enflurane, respectively, these changes were caused by significant increases in GST concentrations at 3 h after anaesthesia (Wilcoxon: group A $P < 0.01$ and group C $P < 0.0001$) and at 6 h following anaesthesia (group C $P < 0.05$). In the patients receiving isoflurane (group B), no significant increase in GST concentrations occurred after anaesthesia. The medians and interquartile ranges of the GST concentrations at times before and after anaesthesia in the three groups are shown in table II. There was no correlation between the changes in GST concentrations and the total dose (duration × maintenance % anaesthetic concentration) of anaesthetic (Spearman rank).

Four patients in group A and three in group C showed secondary increases in GST concentrations, which exceeded the reference range, at

TABLE I. *Demographic data for patients in group A, group B and group C who had normal plasma concentrations of GST, ALT, bilirubin, ALP and GGT before operation*

	Group A Halothane ($n = 22$)	Group B Isoflurane ($n = 18$)	Group C Enflurane ($n = 30$)
Age (yr)			
Mean	42.4	40.2	50.3
SD	17.0	15.8	12.7
Sex (M/F)	11/11	10/8	16/14
Height (m)			
Mean	1.70	1.70	1.71
SD	0.10	0.11	0.12
Weight (kg)			
Mean	70.4	68.6	71.0
SD	13.7	12.2	15.3
Cigarettes (No. day^{-1})			
Median	5	0	0
(1st–3rd quartile)	0–15	0–12	0–10
Alcohol (g week^{-1})			
Median	2.5	6.0	0.1
(1st–3rd quartile)	0.1–15.0	0.7–16.0	0.05–3.0
Duration of anaesthetic (min)			
Median	45	50	45
(1st–3rd quartile)	30–55	33–60	30–55

TABLE II. *Medians (1st–3rd quartile) of GST values (µg litre^{-1}) for groups A, B and C. Significant increases from basal values (Wilcoxon matched-pairs)*: *P < *0.05*; **P < *0.01*; ***P < *0.0001*

	Before anaesthesia	After anaesthesia 3 h	6 h	24 h
Group A Halothane ($n = 22$)	2.9 (2.3–3.4)	3.4** (2.6–4.1)	3.3 (2.2–4.0)	2.5 (1.8–3.5)
Group B Isoflurane ($n = 18$)	2.9 (2.0–3.3)	2.6 (2.1–3.3)	2.6 (2.1–3.1)	2.0 (1.7–2.4)
Group C Enflurane ($n = 30$)	2.4 (1.9–3.0)	3.0*** (2.3–3.4)	2.9* (2.4–3.3)	2.3 (1.4–2.7)

24 h after anaesthesia. One of the patients who had an increased plasma GST concentration at 24 h after anaesthesia with halothane also had an increased plasma ALT activity (116 u. litre^{-1}) at this time. The changes in GST from preoperative concentrations in the samples obtained after anaesthesia, for all three groups of patients, are shown in figure 1.

Many patients, particularly in groups A and C, showed concentrations of GST which exceeded the upper reference value after anaesthesia (fig. 2). The incidence of abnormal GST concentrations following anaesthesia in all three groups is shown in table III. Patients receiving halothane had a greater incidence of abnormal GST concentrations than those receiving enflurane or isoflurane (four-fold table test: $P < 0.01$ and $P <$

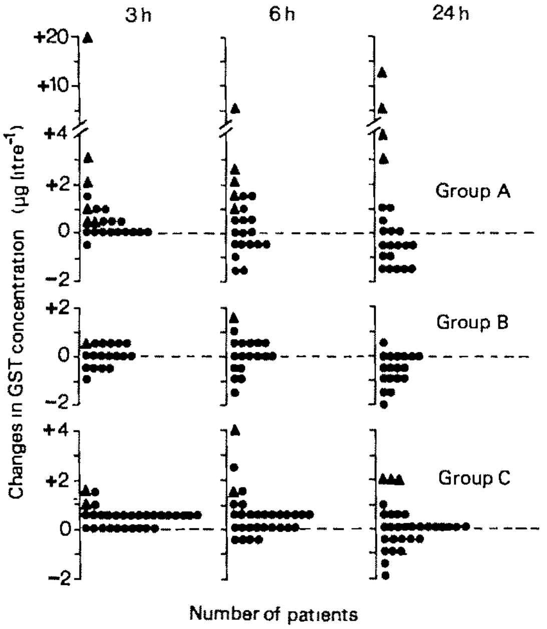

FIG. 1. Individual changes in plasma GST concentrations (µg litre^{-1}) from the preoperative sample. ● = Changes within the reference range; ▲ = increase in GST which exceeded the upper limit of the reference range (4.0 µg litre^{-1}). Group A patients were anaesthetized with halothane, group B patients received isoflurane and group C patients received enflurane.

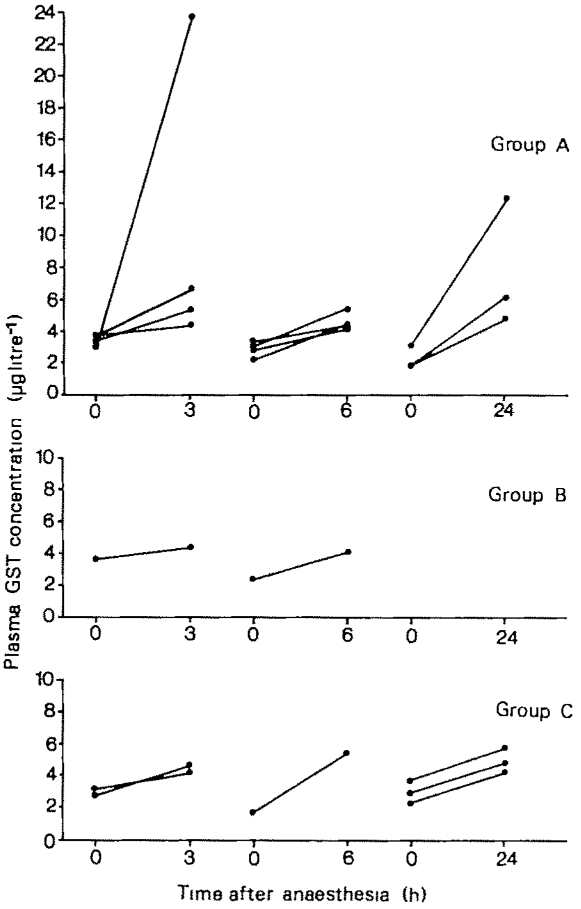

FIG. 2. Abnormal plasma GST concentrations (> 4.0 µg litre^{-1}) following anaesthesia with halothane (group A), isoflurane (group B) or enflurane (group C) compared with concentrations in preoperative samples. The maximum increase in GST concentration for each patient is shown.

TABLE III. *Incidence of abnormal plasma GST concentrations following anaesthesia in patients in groups A, B and C*

GST (µg litre^{-1})	Group A Halothane ($n = 22$)	Group B Isoflurane ($n = 18$)	Group C Enflurane ($n = 30$)
Normal (< 4 0)	11	16	24
Increased (> 4.0)	11	2	6

0.05, respectively). There was no significant difference in the incidence of abnormal GST concentrations between the groups receiving enflurane or isoflurane.

DISCUSSION

We have demonstrated marked differences in the plasma GST response to three halogenated anaesthetic agents. These differences were not attributable to patient selection, since the three patient groups were comparable with respect to factors such as age, sex, alcohol intake and the type and duration of operation. Significant increases in GST concentrations at approximately 3–6 h following anaesthesia were observed with halothane and enflurane, but not isoflurane. These findings are in agreement with the results obtained from a previous study in which only halothane and isoflurane anaesthesia were studied [14].

Changes in GST concentrations result from an impairment in hepatocellular integrity and may be an indication of mild subclinical liver damage of a transient nature. Although the increases in plasma GST were small, a large number of abnormal concentrations were recorded, particularly in the halothane group. In addition, secondary and more marked increases in GST concentrations were seen 24 h after anaesthesia in a few of the patients who had received halothane or enflurane. This secondary phase of impaired hepatocellular integrity was also apparent in previous studies [13, 14]. None of the patients who had received isoflurane showed this secondary increase in concentration.

The relationship between the impairment of hepatocellular integrity that we have observed in the majority of individuals following halothane and enflurane anaesthesia and the rare development of fulminant hepatitis is unclear. Two distinct forms of liver damage, mild (type I) and severe (type II), have been defined following halothane anaesthesia [16]. Hepatic dysfunction of the type I form is probably more common and it is thought to be associated with increased concentrations of serum transaminases [17]. However, not all studies have demonstrated an increased incidence of liver enzyme disturbance following halothane in comparison with other agents, and small, reversible changes in liver function are common following all kinds of anaesthesia [18]. Fulminant hepatic failure following halothane (type II) is a much rarer event which occurs mainly in adults with an incidence of between 1:7000 and 1:30000 [6].

A number of mechanisms have been proposed to account for the hepatotoxic effect of anaesthesia. Biotransformation with the formation of toxic metabolites which may bind to cellular macromolecules and cause necrosis has been suggested [19, 20]. The reductive metabolism of halothane, which is associated with hepatic necrosis in animal models [21], has been demonstrated in man [22]. The degree of biotransformation of the three anaesthetics included in this study differs. Halothane is metabolized to a greater extent (approx. 20% of an inhaled dose) than enflurane (2%) and isoflurane (0.2%) [5]. It is interesting to find that anaesthesia with halothane resulted in a significantly greater incidence of abnormal GST concentrations than did anaesthesia with either enflurane or isoflurane.

The incidence of hepatitis increases with repeated halothane exposure, which would be in keeping with a hypersensitivity reaction. It is of interest that hapten formation involving halothane or a metabolite has been described [4]. There is also evidence to suggest a susceptibility factor responsible for a genetic predisposition to halothane hepatitis in certain individuals [3]. Hepatic hypoxia *per se* has also been implicated in anaesthesia-associated hepatotoxicity [23].

The data presented provide evidence for two phases of mild transient hepatotoxicity after anaesthesia with halothane or enflurane, but not with isoflurane. The first phase occurred in the majority of individuals within 3–6 h of administration of the anaesthetic. In the patients receiving halothane, this is most likely to be caused by the direct specific effect of this agent on hepatic blood flow producing relative tissue hypoxia [24]. However, an increase of GST was also observed in patients receiving enflurane, which is not known to affect hepatic arterial blood flow.

The second phase of impaired hepatocellular integrity, at 24 h, which was indicated by marked changes in GST concentrations in a small number of patients and an increased ALT activity in one patient, may result from the production of toxic metabolites. The changes in GST concentrations seen at this time support evidence for the existence of the mild form of liver damage following halothane (type I) that has been defined by other workers [17]. The proportion of patients showing this response was greater in the group who received the more extensively metabolized anaesthetic halothane, than in the group who had received enflurane.

Changes in plasma GST concentrations clearly demonstrate the stages of hepatotoxicity which may follow anaesthesia. Their measurement may help in the understanding of the mechanisms involved in the hepatotoxicity related to the inhalation of certain volatile anaesthetic agents.

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PLASMA PRILOCAINE CONCENTRATIONS AFTER THREE TECHNIQUES OF BRACHIAL PLEXUS BLOCKADE

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SUMMARY

Brachial plexus blockade (n = 30: 10 axillary, 10 perivascular subclavian, 10 interscalene) was performed on 28 patients, using 35 ml of 1.5% prilocaine in plain solution. Plasma prilocaine concentrations were measured at intervals over the following 60 min. There was no significant difference in the prilocaine concentrations between the three groups. One asymptomatic patient in the interscalene group had a peak prilocaine concentration greater than the accepted threshold for toxic symptoms.

Although a number of specific techniques have been described, injection of local anaesthetic to the brachial plexus is performed essentially in three areas: between the scalene muscles, over the first rib, and in the axilla. Injection at each of these points produces blocks which vary in distribution, but every technique requires a relatively large dose of local anaesthetic. Thus knowledge of the systemic drug concentrations which are likely to result is essential.

Most previous work has considered the effects of using one drug for one particular technique. Where comparisons can be made with the results of a study in which a number of drugs were injected by the interscalene technique, there is a suggestion that this method results in higher systemic concentrations than others [1]. Therefore, a study was devised to allow comparison of the systemic concentrations produced by three different techniques of brachial plexus blockade.

PATIENTS AND METHODS

Patients (ASA I–III) who were to undergo hand or wrist operations under brachial plexus blockade gave informed consent for the study. After an overnight fast and premedication with diazepam 10 mg by mouth, the patient was transferred to the operating theatre and a cannula placed in a vein in the contralateral antecubital fossa for blood sampling. A control sample (time 0) was taken.

Patients were allocated to receive 15% plain prilocaine 35 ml by the interscalene, subclavian perivascular, or axillary techniques [2]. The interscalene route was not used in those patients undergoing surgery predominantly of the ulnar side of the hand. Blood samples were taken into lithium–heparin tubes at 5, 10, 15, 20, 25, 30, 45 and 60 min after the end of the injection and were centrifuged and the plasma withdrawn and frozen in plain tubes pending subsequent analysis. Prilocaine concentrations were measured by high performance liquid chromatography (HPLC). Thirty minutes after the injection, supplementary nerve blocks using lignocaine were performed, as necessary; i.v. sedation was given if needed, and surgery commenced.

Measurement of prilocaine concentration (HPLC)

Plasma 0.25 ml, internal standard solution (ethylmethylglycinexylidide) 50 µlitre, 100 µg ml^{-1}, NaOH 200 µlitre, 1 mol $litre^{-1}$ and diethylether 5 ml were vortexed (1 min), centrifuged (5 min, 3000 rev min^{-1}) and the ether layer transferred to a conical tube. After evaporation to dryness at 35 °C, the residue was reconstituted in 200 µlitre of mobile phase (12:88 acetonitrile/water plus triethylamine/orthophosphoric acid to pH 3.0) and injected to a Novopac column within a Z-module (Waters Ltd) and with a C-18 Guard-

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Pac pre-column. The flow rate was set at 1.5 ml min^{-1} with u.v. detection at 245 nm. Retention times were 8 min for the internal standard and 14 min for prilocaine. The chromatographic conditions were selected to prevent interference from lignocaine present in some of the samples. Calibration graphs of peak:height ratios against prilocaine concentration were linear over the range 0.5–4 μg ml^{-1} and passed through the origin. At the lowest concentration the coefficient of variation of the assay was 5% ($n = 10$).

Statistical analyses were performed by Students unpaired *t* test and Kruskal–Wallis one way analysis of variance by ranking order.

RESULTS

Thirty brachial plexus blocks (10 interscalene, 10 subclavian perivascular, 10 axillary) were carried out on 28 patients for the operations shown in table I. There were no significant differences between the three groups in height, weight or age (table II). Thirteen of the 28 patients were receiving drug therapy for rheumatoid arthritis.

TABLE I. *Type of surgery carried out under three techniques of brachial plexus block: number of patients*

	Inter-scalene	Sub-clavian	Axillary
Release of Dupuytren's contracture	4	1	3
Hand or wrist operations (rheumatoid arthritis)	4	6	3
Miscellaneous	2	3	4

TABLE II. *Mean (SD) heights, weights and ages of patients in each group* n = *Number of patients*

	Interscalene ($n = 10$)	Subclavian ($n = 10$)	Axillary ($n = 10$)
Height (cm)	170.6 (5.8)	170.4 (12.0)	169.3 (5.6)
Weight (kg)	65.0 (8.9)	67.3 (17.9)	66.7 (6.9)
Age (yr)	46.7 (16.9)	55.6 (7.8)	47.3 (15.2)

Table III shows the mean (SD) plasma drug concentrations at each sampling time, together with the mean maximum concentration, for each group. There were no significant differences between the three groups at any time ($P > 0.7$). Figure 1 shows the mean prilocaine concentrations plotted against time. The axillary and subclavian perivascular groups demonstrated similar drug concentrations: these increased during the first 15 min to a peak concentration which was sustained for a further 15 min. The interscalene group had a similar increase in concentration during the first 15 min, but reached a higher peak concentration at 20 (and again at 25) min. The higher concentrations at 25 and 30 min in the interscalene group were almost entirely because of one patient who had plasma concentrations of 10.94 μg ml^{-1} and 8.04 μg ml^{-1} at 20 and 25 min, respectively.

The mean (±SD) areas under the curve (AUC (0,60)), by linear trapezoidal rule, were not significantly different between groups: interscalene = 115±59 μg ml^{-1} min; subclavian = 97±34 μg ml^{-1} min; axillary = 104±44 μg ml^{-1} min. On analysis, the statistical power of the study to detect 20% differences in the AUC (0,60) at a *P* level of 0.05 in a two-tailed test was > 80%.

DISCUSSION

Prilocaine was used in this study because its low systemic toxicity makes it the agent of choice for medium duration procedures when a large dose of local anaesthetic is required. Winnie [3] recommended a volume of 0.5 ml for each inch

TABLE III. *Plasma prilocaine concentrations (μg ml^{-1}, mean ± SD) after three techniques of brachial plexus block. Mean max. = mean of the highest value in each patient irrespective of time. Differences between techniques were not significant*

	Time (min)								Mean max
	5	10	15	20	25	30	45	60	(range)
Interscalene	1.36 (0.74)	1.93 (0.88)	2.17 (1.08)	2.75 (1.51)	2.76 (2.98)	2.46 (2.14)	1.86 (0.98)	1.33 (0.8)	3.61 (0.44–10.94)
Subclavian perivascular	0.99 (1.08)	1.49 (0.95)	1.83 (1.05)	1.87 (1.22)	1.89 (1.27)	1.86 (0.63)	1.66 (0.62)	1.66 (0.82)	2.74 (0.11–4.9)
Axillary	1.57 (1.72)	1.89 (1.54)	2.00 (1.23)	1.81 (0.77)	1.92 (1.00)	1.99 (1.27)	1.82 (0.78)	1.44 (0.63)	2.78 (0.19–5.24)

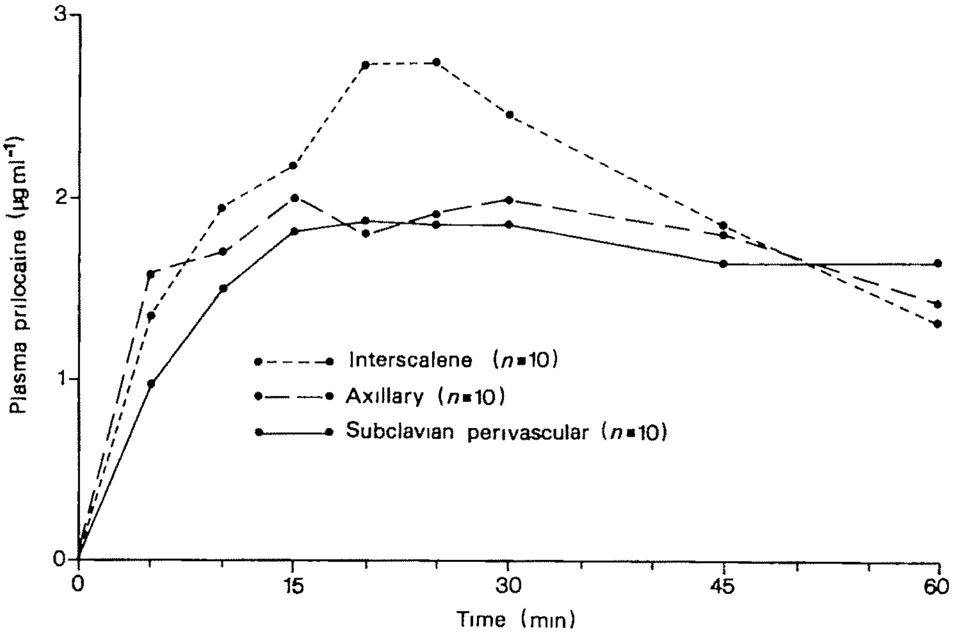

FIG. 1. Mean plasma concentrations of prilocaine after brachial plexus block with 1.5% plain prilocaine 35 ml.

(2.54 cm) in height for adequate brachial plexus blockade. In this study, the mean height was 5 feet 6 inches (167.6 cm) and, therefore, the 35-ml volume of injection (our standard volume) was appropriate.

The results suggest that there was no difference in the rate of absorption of prilocaine from the different sections of the brachial plexus. The range of results was wide (as shown in table III), and one patient in the interscalene group developed a peak concentration of 10.94 µg ml^{-1}. The timing of this does not suggest i.v. injection and the patient did not develop any clinical signs of toxicity. However, it has been suggested that the threshold for toxicity of prilocaine is 6 µg ml^{-1} [4] and, therefore, there is no room for complacency when using prilocaine in the above dosage.

We found no correlation between the plasma prilocaine concentrations and either the height or weight of the patients. In addition, the results of this study (in which many patients had rheumatoid arthritis) are similar to those found by Wildsmith and colleagues [1] in a much younger and healthier population. There was no evidence to suggest a greater risk of toxicity in patients with rheumatoid disease.

Since the systemic concentrations of prilocaine after interscalene, subclavian perivascular, or axillary injection were similar, we conclude that the choice of route should be governed by the experience of the anaesthetist and the extent of block required [5]. However, it should be noted that one patient in the interscalene group developed unexplained and high systemic concentrations of local anaesthetic at 25 and 30 min after injection. This was an important occurrence and supports those who believe that brachial plexus blockade should not be performed by the non-anaesthetist [6].

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LACK OF CORRELATION BETWEEN THE ANAESTHETIC AND ANTI-CONVULSANT POTENCIES OF ALTHESIN, KETAMINE AND METHOHEXITONE

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SUMMARY

Using Sprague–Dawley rats, the anti-convulsant potencies of Althesin, ketamine and methohexitone were determined for bicuculline- and strychnine-induced seizures and compared with their effects on hyperbaric seizures. All three anaesthetics protected against both types of chemical convulsants; the degree of protection varied from 34 to 151 %, with Althesin being the most effective. However, there was no correlation between their anti-convulsant and anaesthetic potencies, and no relationship between the effects on chemical convulsions and the interactions of the same agents with hyperbaric convulsions. These data suggest that the order of anti-convulsant potencies at equivalent anaesthetic concentration is Althesin ≫ ketamine = methohexitone, and that neither bicuculline- nor strychnine-induced seizures are a good model for hyperbaric convulsions.

The convulsant/anti-convulsant properties of different anaesthetics are of clinical importance and of mechanistic interest. For example, much has been written for and against the use of Althesin, ketamine and methohexitone in patients with status epilepticus [1–3]. However, less is known about anaesthetic interactions with chemically-induced convulsions, and there have been relatively few systematic comparative studies. Certain anaesthetics are known to provide good protection against hyperbaric convulsions [4], but little is known about the basis of these effects.

In the present study the two chemical convulsants selected were bicuculline and strychnine: bicuculline is a γ-aminobutyric acid (GABA) receptor antagonist thought to act directly on one of the types of GABA receptors; strychnine blocks the inhibitory action of glycine at postsynaptic receptors in the spinal cord and the (antagonizing) feedback inhibition by Renshaw cells on α-motor neurones. Althesin, ketamine and methohexitone were selected as the anaesthetics for this study because their interactions with hyperbaric-induced convulsions had been investigated previously [5, 6], and because they were representative of the different types of i.v. agents. Some of the anti-convulsant effects of the inhalation anaesthetics have been documented [7]; results suggest that halothane and enflurane have a protective effect against convulsions associated with reduced GABAergic transmission.

The present study was intended to test the hypothesis that there is a correlation between the anaesthetic and anti-convulsant potencies of the i.v. agents. Evidence suggesting such an hypothesis includes the work on mice, selectively bred for resistance to nitrous oxide anaesthesia, which demonstrated that they were significantly more sensitive to strychnine and pentylenetetrazol convulsions (but not bicuculline convulsions) than those bred for susceptibility to nitrous oxide anaesthesia [8]. Evidence against the hypothesis includes the lack of correlation between the structure–activity relationships governing anaesthesia *per se* and those related to convulsant activity or central nervous system irritability [9]. Finally, there is no *a priori* reason for assuming that the anaesthetics have equal anti-convulsant potencies, even if it could be demonstrated that

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that pharmacological property for a particular agent was closely related to its anaesthetic action. These experiments were designed to study any relationship between anaesthetic and anti-convulsant potency.

MATERIALS AND METHODS

A total of 44 female Sprague–Dawley rats (mean weight 245 g, SD 35) were used. These were supplied from a specified pathogen-free breeding unit; the corresponding age range was 8–12 weeks (young adults). A 24-gauge "Abbocath" was inserted to the lateral tail vein under 1% halothane in oxygen anaesthesia and was taped securely in place. A double-lumen catheter was connected to the Abbocath to permit simultaneous infusion of both anaesthetic and convulsant.

Three i.v. anaesthetics were studied: Althesin (alphaxalone/alphadolone acetate in Cremophor EL; Glaxo Ltd); ketamine (Ketalar; Parke Davis Ltd) and methohexitone sodium (Brietal; Lilly & Co. Ltd). The anaesthetic was infused from a small infusion pump (MS 16, Graseby Dynamics Ltd) and each rat was maintained at a constant infusion rate for a minimum of 15 min to ensure that the anaesthetic depth was stable. Anaesthesia was assessed in terms of a moderate abdominal twitch response to a 10-V electrical stimulus applied to the tail. The infusion rate was varied in each animal until this response was just prevented. The temperature of the anaesthetized rats was measured with a rectal thermistor probe and maintained at 37 ± 1 °C with a heating mat.

Bicuculline (Sigma) was dissolved in hydrochloric acid 0.1 mol litre^{-1} and titrated back to pH 3.0 with sodium hydroxide 10 mol litre^{-1}. A stock solution of 1 mg ml^{-1} was prepared and frozen in 1-ml aliquots. It was diluted immediately before use with 0.9% saline to give a final concentration of 0.1 mg ml^{-1}. Strychnine (Sigma) was dissolved in distilled water to give a stock solution of 25 mg ml^{-1}. This was frozen in 1-ml aliquots and diluted with saline on the day of the experiment to give a final concentration of 2.5 mg ml^{-1}.

After 15 min of anaesthesia, either bicuculline or strychnine was infused via a Braun "perfusor" pump (rate of infusion 1.62–1.67 ml min^{-1}). The time taken to reach the end-point was recorded; for bicuculline this was the first myoclonic jerk, as full seizures did not always occur in the presence of Althesin. For strychnine, the end-point used was the first full convulsion, as this was the first unambiguous sign of the desired effect of the drug.

TABLE I. *The amount of bicuculline or strychnine required (mg kg^{-1}) for the convulsion end-point. The data were compared with the Mann–Whitney* U *test* ***$P < 0.005$, **$P < 0.01$, *$P < 0.05$

Convulsant	Control	Althesin	Ketamine	Methohexitone
Bicuculline				
Mean	0.505	1.28***	0.665**	0.720***
SEM	0.03	0.17	0.02	0.04
n	8	5	5	5
Strychnine				
Mean	1.00	2.60**	1.48*	1.34*
SEM	0.04	0.25	0.11	0.06
n	4	6	6	5

Control animals received convulsant alone. They were placed in a small restraining cage, and a minimum of 15 min was allowed for recovery from the insertion of the catheter before the convulsant was infused. Each rat was used once and, when the convulsant end-point was reached, was rapidly killed with an overdose of Althesin. Both pumps were accurately calibrated after each experiment. Results were calculated as mg kg^{-1} of convulsant required. All statistical comparisons used the Mann–Whitney *U*-test, to avoid any assumptions about the distribution of the data.

RESULTS

The anaesthetic potencies were measured as the minimum infusion rates necessary to achieve anaesthesia in the individual animals. These data were then combined for each anaesthetic group to determine the mean infusion rates (±SEM) which were as follows: Althesin (total steroid content) 0.607 (±0.010) mg kg^{-1} min^{-1}, $n = 11$; ketamine 2.08 (±0.015) mg kg^{-1} min^{-1}, $n = 11$; and methohexitone 1.10 (±0.024) mg kg^{-1} min^{-1}, $n = 10$.

The convulsant doses of either bicuculline or strychnine were measured either in control animals or in anaesthetized animals and then combined to estimate the mean amount of convulsant required in each group (preliminary experiments demonstrated that the vehicle for Althesin (Cremophor EL) had no effect on the convulsant end-point). These data, together with the statistical comparisons between the means, are presented in table I. The anti-convulsant potencies, at equivalent anaesthetic concentrations, were calculated

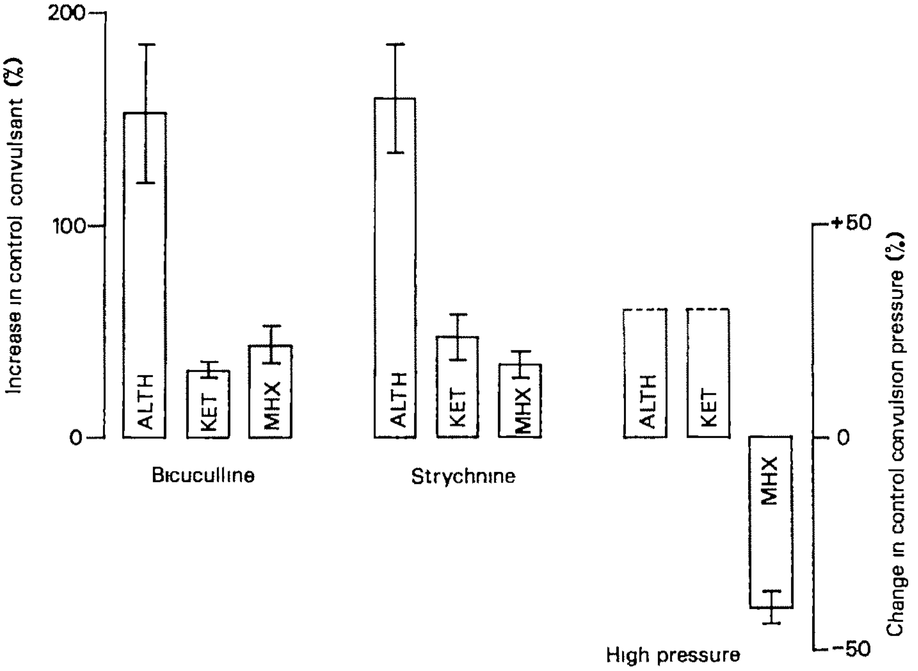

FIG. 1. The percentage increase in either bicuculline or strychnine requirement (compared with control values) in the presence of Althesin (ALTH), ketamine (KET) or methohexitone (MHX). For comparison the interactions of the same agents with high pressure convulsions are also plotted in terms of the percentage change in convulsion pressures relative to control values. (Hyperbaric data from Green, Halsey and Wardley-Smith [5].)

as the percentage inceases in convulsant required in the presence of anaesthetic relative to awake control data; these are shown in figure 1 (left-hand side).

The lack of correlation between anaesthetic and anti-convulsant potencies is demonstrated in figure 1; thus, despite the anaesthetics being at equivalent anaesthetizing concentrations, the degree of anti-convulsant activity was not the same. Althesin was three to four times more effective than either ketamine or methohexitone in increasing the chemical convulsion thresholds ($P < 0.01$). Ketamine and methohexitone provided protection against both types of convulsion, but were not significantly different from each other for either convulsant. Figure 1 also includes data for anaesthetic protection against hyperbaric convulsions [5, 6], which is considered in the Discussion section.

DISCUSSION

The mean anaesthetizing infusion rates were in agreement with those determined in previous studies [10]. The relationships between infusion rate and plasma or tissue concentration depend on the different pharmacokinetics of the different agents. For this reason, the present study was designed to measure the relative anti-convulsant activities at the same depth of anaesthesia—as determined by a standardized behavioural response (as distinct from a fixed plasma drug concentration). Assessment of the dose of anaesthetic required for each animal was necessary because the steep dose–response curves for the anaesthetics meant that the use of a simple fixed concentration would have resulted in inadequate anaesthesia in some animals and excessive depth of anaesthesia in others. The stimulus–response that we have used had already been demonstrated to be consistent [11] and, for these agents, corresponded to relatively deep anaesthesia. There is a difficulty that it may reflect analgesia rather than anaesthesia, but it was chosen because previous studies have demonstrated that the method is analagous to the noxious stimuli and gross muscular responses used in the assessment of clinical anaesthesia [12].

It is clear from the convulsion thresholds that the three anaesthetics did not possess equal anticonvulsant potency against the different types of convulsion studied. Althesin, ketamine and methohexitone provided significant protection against both bicuculline- and strychnine-induced seizures, but the amount of protection conferred in the presence of equivalent anaesthetic concentrations was not the same for all the anaesthetics. Althesin showed the greatest protective effect against convulsions produced both by bicuculline and strychnine (fig. 1). Methohexitone and ketamine increased the amount of convulsant required by between only 30 and 50% of control, although this was still significant for both convulsants.

For comparison, the interactions of Althesin, ketamine and methohexitone with hyperbaric convulsions [5, 6] have been included in figure 1, plotted in terms of the percentage increase in convulsion threshold pressures in the anaesthetized animal. The data on the hyperbaric and chemical convulsions are not directly comparable because the rats, although of the same strain, came from different populations. Nevertheless, the *relative* effectiveness of the three anaesthetics on each type of convulsion indicates a totally different pattern for hyperbaric convulsions (fig. 1). Both Althesin and ketamine increased the pressures at which convulsions occurred above the maximum working pressure of the hyperbaric chamber (100 ATA). In contrast, methohexitone actually reduced the threshold pressure to 60% of the control value. These data are not what would have been expected from the apparent additivity of strychnine and hyperbaric convulsions [13].

The mechanism whereby Althesin shows a greater effect than ketamine or methohexitone against bicuculline and strychnine convulsions is not clear. It is also not clear why, when ketamine and methohexitone are approximately equally effective against bicuculline and strychnine, they should have such different actions at high pressure. Althesin may act by enhancing GABAergic or glycinergic inhibitory transmission or both types, since it was equally effective against both bicuculline and strychnine. Potentiation of the effects of GABA has been demonstrated [14]. It has also been shown to protect against other types of convulsion, such as hyperbaric oxygen convulsions [1] which are thought to result from disordered GABA metabolism [15]. Althesin also protects against focal epileptic discharges produced by the topical application of penicillin G [1], a GABA receptor antagonist. However, the profound anti-convulsant activity of Althesin is unlikely to depend wholly on its action on GABA, since both ketamine and methohexitone are thought to have significant effects on GABA transmission.

The relative ineffectiveness of ketamine as an anti-convulsant is consistent with previous studies. Thus ketamine failed to lower the minimum electroshock seizure threshold in mice [16], and there was only an insignificant effect of ketamine on strychnine-induced seizures in mice [17]. In neurochemical studies it has been shown that ketamine potentiated the effects of GABA at its receptor site [18]. Accumulation of GABA in the synaptic cleft has been proposed as a possible mechanism of action for the anaesthetic/anticonvulsant properties of ketamine [19].

Enhancement of GABA-mediated post-synaptic inhibition has been proposed as a mechanism, at least in part, for barbiturate anaesthesia [20]. It has also been shown that pentobarbitone and thiopentone reversed the antagonistic effects of bicuculline and strychnine on GABA- and glycine-mediated inhibition, respectively [21].

The interactions of these anaesthetics with convulsants may also involve an effect on excitatory neurotransmission. Ketamine has been shown to reduce selectively excitation produced in central mammalian neurones by N-methylaspartate (NMA) [22]. With the same preparation (cat spinal neurones), methohexitone was found to have no effect on excitation produced by NMA; however, it enhanced GABA- but not glycine-mediated inhibition [23]. It is possible that this effect on excitatory neurotransmitters could partially explain the considerable differences seen between the actions of anaesthetics on hyperbaric convulsions; it has been shown that antagonists of excitatory amino acid neurotransmitters provide good protection against the HPNS [24, 25].

In addition to the differential effects of the anaesthetics, the three types of convulsions (as observed in control animals by ourselves and others) have different behavioural characteristics. Bicuculline causes myoclonic jerking followed by clonic convulsions. Tonic seizures have rarely been reported and only with high (lethal) doses. Strychnine convulsions are characterized by a tonic extension of the body and of all limbs—little or no clonic activity has been observed [26]. The classical description of a strychnine convulsion includes the tonic extension being preceded (and followed during the phase of postictal depression) by phasic symmetrical extensor thrusts that may be initiated by any modality of sensory stimulus [27]. There is no evidence of tremor preceding strychnine-induced convulsions even when subconvulsive doses are used [28]. In contrast with these chemical convulsants, hyperbaric convulsions have very different characteristics. In rats the convulsions are either a combined clonic-tonic type, or just clonic. They are preceded at lower pressures by tremor and myoclonus.

In conclusion, there is no correlation between the anaesthetic and anti-convulsant potencies of Althesin, ketamine and methohexitone. This lack of correlation applies both to bicuculline- and strychnine-induced seizures and is in agreement with the previous study on hyperbaric convulsions. These results suggest that:

(1) The differences that we have shown in the anti-convulsant potencies of these agents suggest that care should be taken when selecting an anaesthetic for patients with seizure disorders. The present data indicate that the anti-convulsant potential under equivalent anaesthetic conditions is Althesin $\gg$ ketamine = methohexitone.

(2) The three anaesthetics have differences between them in their neurochemical actions on both the GABAergic and glycinergic systems, which may contribute to their different anti-convulsant actions.

(3) Neither the bicuculline- nor the strychnine-induced seizure is an adequate model for hyperbaric-induced convulsions.

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PHARMACOKINETICS OF PROPOFOL (DIPRIVAN) IN ELDERLY PATIENTS

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SUMMARY

The pharmacokinetics of propofol (2,6 diisopropylphenol) were compared in 12 patients aged 65–80 yr and 12 patients aged 18–35 yr. After premedication with papaveretum i.m., anaesthesia was induced with propofol 2.0 mg kg^{-1} in the elderly and 2.5 mg kg^{-1} in the younger patients. Alcuronium 12–20 mg was then given and the patient's lungs ventilated with halothane and nitrous oxide in oxygen. Blood was taken after various time intervals up to 24 h for the measurement of propofol concentrations by HPLC and for the estimation of propofol protein binding. The mean blood propofol concentration was generally higher in the elderly group, but this difference was only significant at 2 min after induction. The clearance of propofol was significantly lower in the elderly (1.44 ± 0.10 (SE) litre min^{-1}) than in the younger patients (1.79 ± 0.12 litre min^{-1}). The volume of the central compartment in the elderly patients was significantly smaller (19.6 ± 5.2 litre) than that in the young (26.3 ± 2.9 litre). There was no difference in the volume of distribution at equilibrium (1608 ± 246 litre in the elderly and 1757 ± 360 litre in the young), in the volume of distribution at steady state (691 ± 139 litre in the elderly and 771 ± 236 litre in the young) or in the half-lives of distribution and elimination. The plasma protein binding of propofol was similar in both groups and showed no trend with time after dose.

In elderly patients there is a tendency for total body water, cardiac output and hepatic blood flow to be lower than in young patients [1]. Pharmacokinetic studies of thiopentone [2,3] methohexitone [4] and etomidate [5] have shown significant changes with ageing. We have compared the pharmacokinetics of propofol (2,6 diisopropylphenol) in elderly and young patients.

PATIENTS AND METHODS

Twenty-four patients were studied: 50% were aged 65–80 yr, the remainder being 18–35 years old. All patients were ASA grade I–II and gave informed consent to the study. All patients underwent surgery under general anaesthesia. Hospital Ethical Committee approval was obtained.

Patients were premedicated with papaveretum 10–20 mg i.m. 1 h before surgery; hyoscine 0.2–0.4 mg was given if an anti-sialagogue was indicated. An 18-gauge cannula (for venous sampling) was inserted to a vein in the antecubital fossa. A 23-gauge "Butterfly" needle was placed in a vein on the dorsum of the contralateral hand for administration of drugs. Anaesthesia was induced with the aqueous emulsion formulation of propofol (Diprivan) 2.5 mg kg^{-1} in the younger patients and 2.0 mg kg^{-1} in the elderly patients; the injection was given over 30 s. Time 0 was taken to be when the injection was completed.

When present, the severity of pain on injection of propofol was noted, and the intensity was assessed as mild, moderate or severe. Any evidence of excitatory phenomena on induction of anaesthesia was recorded. When anaesthesia had been induced successfully 67% nitrous oxide and 0–1% halothane in oxygen were administered using an anaesthetic face mask. Alcuronium

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12.5–20 mg was given and when muscle paralysis was satisfactory the trachea was intubated; the patients' lungs were then ventilated to normocapnoea according to the Radford nomogram. No other drugs were given during the operation. At the end of surgery neostigmine 2.5 mg was given (with atropine 1.2 mg) to antagonize neuromuscular blockade. During anaesthesia the arterial pressure and heart rate were monitored. Papaveretum and prochlorperazine were given, when necessary, in the postoperative period.

Blood was taken for whole blood propofol estimation before injection, and after the end of the propofol injection at the following times: 2, 4, 6, 8, 10, 15, 20, 30, 45, 60, 75, 90, 120 and 150 min and 3, 4, 5, 6, 7, 8, 10, 12, 18 and 24 h. Each 5-ml sample was thoroughly mixed in tubes containing potassium oxalate and stored at +4 °C until assayed. Additional blood samples (10 ml) were taken approximately 10 and 120 min following the injection for estimation of propofol plasma protein binding. After thorough mixing in tubes containing potassium oxalate, these samples were centrifuged, the plasma removed and stored in plain tubes at +4 °C until required for analysis.

Propofol concentrations in the samples of blood and plasma were determined by a modification of the method described by Adam and colleagues [6]. The cyclohexane extract was basified with tetramethylammonium hydroxide and then evaporated to dryness under nitrogen. After reconstitution, the residue was subjected to high pressure liquid chromatography with fluorescence detection. The limit of detection was 2 ng ml^{-1} with an interbatch coefficient of variation of 8 % over the concentration range observed in this study.

Pharmacokinetic analysis of each data set was performed using the extended least squares curve fitting programme ELSFIT [7]; initial parameter estimates were derived using STRIPE [8].

The degree of binding of propofol to plasma proteins was estimated using a "Dianorm" equilibrium dialysis apparatus. Aliquots of plasma (1 ml) were dialysed for 4 h against 1 ml of phosphate buffer 0.067 mol $litre^{-1}$, pH 7.4, containing 0.9 % w/v sodium chloride. Weighed aliquots of dialysis buffer were then analysed for propofol content using the method described for whole blood.

The blood propofol concentrations at each time interval and the derived pharmacokinetic parameters were found (by plotting the data on Normal distribution paper) to follow a skewed distribution. Therefore, we used a non-parametric test (the Wilcoxon Rank Sum Test) to determine the significance of differences between the two groups; the minimum level of statistical significance was taken as $P < 0.05$.

RESULTS

The demographic details of the two groups of patients are shown in table I.

Anaesthesia was induced smoothly in all patients. Excitatory phenomena were not seen and there were no involuntary muscle movements. Mild or moderate pain on injection was experienced by three elderly and four of the younger patients; only one patient (from the younger group) considered the pain to be severe. Hypotension (systolic arterial pressure less than 90 mm Hg following induction) occurred in three elderly and one young patient; change in posture and a decrease in the inspired halothane concentration brought about a satisfactory increase in arterial pressure in these patients. All patients recovered swiftly and smoothly from anaesthesia which lasted on average 43 min (range 24–61, SD 11.6 min) in the elderly patients and 45 min (16–140, SD 35.2 min) in the younger group.

Blood concentrations of propofol in the elderly patients were compared after dose correction (by a factor of 5/4) with those in the young. At 2 min after the injection the mean blood concentration of propofol was 6.07 ± 1.08 SEM μg ml^{-1} in the elderly patients and 4.15 ± 0.42 μg ml^{-1} in the younger group ($0.01 < P 0.02$). There were no other significant differences in mean blood propofol concentrations at any time. Figure 1 shows the dose-corrected mean blood propofol concentrations for the two groups.

After visual inspection of the plotted data for each individual a three-compartment open mammalian model with excretion from the central compartment was fitted to each data set. For two elderly patients only two exponential phases could be defined with any confidence and the data for

TABLE I. *Age, weight and height of patients (mean ± 1 SD)*

	Age (yr)	Weight (kg)	Height (m)
Elderly	71.4±4.03	61 8±9.7	1.61±0.09
Young	27.5±5.25	65.7±10.3	1.72±0.08
		ns	$P < 0.05$

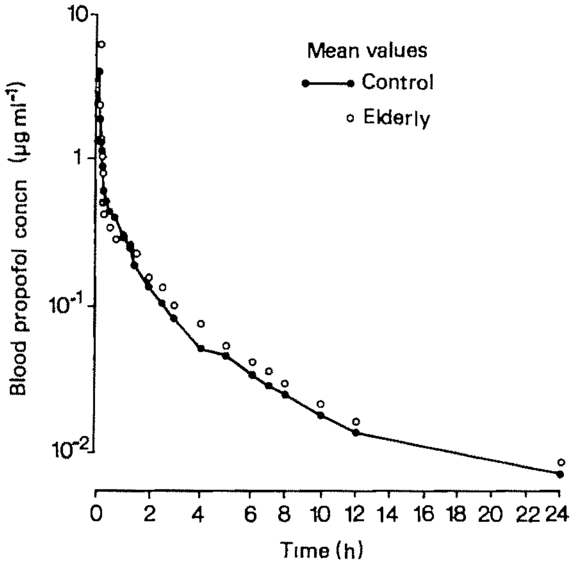

FIG. 1. Mean blood propofol concentrations for young patients and elderly patients after dose correction.

these patients were assumed to conform to a two-compartment model. The half-lives of the three phases ($T_{\frac{1}{2}}^{\alpha}$, $T_{\frac{1}{2}}^{\beta}$, $T_{\frac{1}{2}}^{\gamma}$) the total body clearance (TBC), the volumes of distribution at steady state (V^{ss}) and equilibrium (V^{γ}) and the volume of the central compartment (V) were then calculated using standard equations [9]. As the data were not normally distributed, the Wilcoxon Rank Sum Test was applied for the statistical analysis. The results are shown in table II.

The volume of the central compartment was significantly smaller ($P = 0.046$) in the elderly (19.6 ± 5.2 litre) than in the younger (26.3 ± 2.9 litre) patients. The total body clearance of propofol was considerably lower in the elderly (1.44 ± 0.10 litre min^{-1}) than the young (1.79 ± 0.12 litre min^{-1}) and this difference was also significant ($P = 0.03$). However, when individual data for V and TBC were normalized for body weight there were no statistically significant differences between the two groups. There was no statistical difference in the other pharmacokinetic parameters.

Propofol concentrations in whole blood for individual patients in both groups were similar to those in plasma at the same sampling time. Mean ratios (plasma:whole blood) at 10 min after induction were 1.23 ± 0.11 and 0.97 ± 0.08 for elderly and young patients, respectively. Corresponding ratios at 120 min after induction were 1.47 ± 0.21 and 1.12 ± 0.09.

Propofol protein binding was high: values of 97–99% were obtained at both sampling times. There was no significant difference in protein binding between the elderly and young patients at either sampling time, and there was no apparent trend in the data with time after dose.

DISCUSSION

The pharmacokinetic data for the younger patients show that, while the total body clearance

TABLE II. *Volumes of distribution at steady state* (V^{ss}) *and equilibrium* (V^{γ}); *volume of central compartment* (V); *total body clearance (TBC) and half-lives of the three phases* ($T_{\frac{1}{2}}^{\alpha}$, $T_{\frac{1}{2}}^{\beta}$, $T_{\frac{1}{2}}^{\gamma}$); *rate constants (mean values ± 1 SEM)*

	Young	Elderly	P
V^{ss} (litre)	771 ± 236	691 ± 139	ns
V^{γ} (litre)	1756 ± 360	1608 ± 246	ns
V (litre)	26.3 ± 2.9	19.6 ± 5.2	0.046
TBC (litre min^{-1})	1.78 ± 0.12	1.43 ± 0.09	0.030
$T_{\frac{1}{2}}^{\alpha}$ (min)	2.04 ± 0.27	1.84 ± 0.25	ns
$T_{\frac{1}{2}}^{\beta}$ (min)	52.4 ± 9.2	69.3 ± 8.7	ns
$T_{\frac{1}{2}}^{\gamma}$ (min)	674 ± 122	834 ± 170	ns
V^{ss} (litre kg^{-1})	11.9 ± 3.5	12.4 ± 3.3	ns
V^{γ} (litre kg^{-1}	27.1 ± 5.4	28.4 ± 6.0	ns
V (litre kg^{-1})	0.415 ± 0.055	0.311 ± 0.080	ns
TBC (ml min^{-1} kg^{-1})	27.7 ± 2.3	23.2 ± 1.1	ns
k_{31}	$(1.91 \pm 0.2)10^{-3}$	$(1.63 \pm 0.21)10^{-3}$	ns
k_{10}	$(0.77 \pm 0.09)10^{-1}$	$(1.23 \pm 0.26)10^{-1}$	ns
k_{13}	$(3.91 \pm 0.58)10^{-2}$	$(5.83 \pm 1.19)10^{-2}$	ns
k_{12}	$(2.46 \pm 0.40)10^{-1}$	$(2.95 \pm 0.79)10^{-1}$	ns
k_{21}	$(5.97 \pm 0.97)10^{-2}$	$(3.75 \pm 0.51)10^{-2}$	ns

was very large (mean 1.79 litre min^{-1}), $T_{\frac{1}{2}}^{\gamma}$ was prolonged (mean 674 min), so resulting in a high equilibrium volume of distribution estimate. The mean volume of distribution at steady state was less than half the value for the equilibrium volume of distribution. This suggests that, after a rapid injection of a single dose of propofol, the drug was rapidly cleared from the body, but a small proportion remained in tissue (presumably lipid) and was eliminated much more slowly. It is likely, therefore, that the elimination of propofol during the third exponential phase is constrained by its slow return from the deep to the central compartment. This is confirmed by mean ratios of $k_{31}:k_{10}$, which were 0.0264 ± 0.0029 (SEM) for the young patients and 0.0218 ± 0.0064 for the elderly patients. Elimination during the second exponential phase is probably dominated by the unconstrained metabolic clearance of propofol. Compared with previously published data in patients [10–12] we found the third exponential phase half-life to be relatively prolonged (674 compared with 184–382 min), whereas the half-lives for the first two phases were broadly similar. This difference was probably a consequence of the longer sampling period in our study—previous studies had only sampled for 8–12 h—so enabling the parameters of the third phase to be determined with more confidence. However, even in the present study the sampling period was shorter than desirable (only about double $T_{\frac{1}{2}}^{\gamma}$).

The reduction in dose requirements of thiopentone in elderly patients has been well documented [13]; a similar phenomenon is recognized for other i.v. induction agents. It would, therefore, be surprising if the same did not hold true for propofol and, in fact, more recent work [14, 15] confirmed that the propofol dose requirements are also age-related.

We found that the initial blood concentration of propofol (at 2 min) was significantly higher in the elderly than the younger patients. This was a consequence of the significantly lower initial distribution volume in the elderly, which is consistent with a reduction in the volume of highly perfused tissues relative to body mass or a reduced perfusion of these tissues as a consequence of the documented [1] lower cardiac output in elderly patients. Similar trends have been observed for thiopentone [2] and etomidate [5], but no age-related differences in V were seen for fentanyl and alfentanil [16]. The relatively high blood concentrations of propofol in the first few minutes following induction of anaesthesia could be implicated in the higher incidence of hypotension which we found in the elderly as compared with the younger patients.

Results from a volunteer study [17] in which a subanaesthetic dose of ^{14}C-propofol was administered suggested that propofol is extensively metabolized before renal elimination—only 0.3 % of the material recovered from the urine was present as unchanged drug. Hence renal clearance would be expected to play little part in the total body clearance of propofol; an interim analysis of a study of the kinetics of propofol in patients with renal failure [18] showed no significant difference in the clearance of propofol in these patients as compared with controls. Our work has resulted in values for total body clearance which approximate to hepatic blood flow. The values for the elderly (1.44 ± 0.10 litre min^{-1}) were significantly lower than those for the controls (1.79 ± 0.12 litre min^{-1})—the age-related decline in hepatic blood flow [19] results in reduced total body clearance of drugs, like propofol, which depend heavily on hepatic metabolism for their elimination.

Similarly, the clearance of etomidate has been shown to be significantly decreased with age, with a decrease of approximately 2 ml kg^{-1} min^{-1} for every decade increase in the 22–82 yr age range. However, thiopentone, the clearance of which is capacity limited, showed no change in clearance with age [2, 3]. The difference (25 %) in the volume of the central compartment for propofol, between the elderly and young patients, is consistent with the reduced induction dose requirement in the former observed by Dundee and colleagues [14]. Furthermore, the 20 % reduction in total body clearance observed in the elderly patients would be expected to result in a slightly smaller propofol maintenance dose requirement in the elderly. Mackenzie and Grant [20] have shown recently that patients older than 65 yr receiving an infusion of propofol for about 1.5 h required an infusion rate significantly less (24 %) than that required by younger subjects.

Although mean values of V normalized for body weight were also 25 % lower in elderly patients, the difference was not statistically significant. Similarly, body weight normalized values of TBC were 16 % lower in elderly patients, but the difference did not reach statistical significance. The reason for this is unclear, but may be the slightly greater inter-individual variability in the data when normalized for body weight.

In conclusion, our work has shown that the initial distribution volume of propofol was lower in elderly compared with younger patients and, as a consequence, propofol concentrations were higher in the elderly immediately following injection. Additionally, the total body clearance of propofol in the elderly was lower than that in the younger patients. These pharmacokinetic differences could be explained by decreases in cardiac output and hepatic blood flow in the elderly.

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UPPER LIMB BLOOD FLOW DURING HEXAMETHONIUM-INDUCED HYPOTENSION

Studies in Patients Anaesthetized with Halothane

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SUMMARY

We report the effect of hypotensive anaesthesia on blood flow in the upper limbs of 17 patients before the start of surgery. Under light halothane–oxygen anaesthesia, patients ($n = 17$) were given hexamethonium 0.5–1.0 mg kg^{-1}. Forearm blood flow (FBF), hand blood flow (HBF) and systemic arterial pressure (AP) were measured before, and 9 and 18 min after the administration of the hexamethonium. During the control period of halothane anaesthesia, HBF was AP-dependent, but FBF was not. Hexamethonium produced a statistically significant ($P < 0.001$) decrease in systolic AP by 9 and 18 min, but significant reductions in FBF and HBF were seen only at 9 min. During the hypotensive period neither HBF nor FBF correlated with the systolic AP, which had decreased from an average of 98 mm Hg to an average of 65 mm Hg (range 95–50 mm Hg), but the changes in HBF and FBF did correlate with the changes in systolic AP. As a secondary factor, the control FBF correlated inversely with the reduction in FBF after hexamethonium. We concluded that hypotension induced by hexamethonium during halothane anaesthesia produced a transient reduction in limb blood flow that was dependent on the change in AP. A range of systolic AP from 95 to 50 mm Hg did not correlate with either FBF or HBF during the hypotensive period.

For many years anaesthetists have used controlled hypotension to minimize blood loss and, in some difficult procedures, to provide the surgeon with a bloodless field. Several investigators [1–5] have reported the effect of hypotensive anaesthesia on blood flows in various organs, but there is little information on how hypotensive anaesthesia affects peripheral blood flow [6]. The object of this study was to assess the effect of controlled hypotension on the blood flow in the forearm and hand of the anaesthetized patient.

PATIENTS AND METHODS

The subjects of this study were one female and 18 male patients who required hypotensive anaesthesia for surgical procedures. Their ages ranged from 27 to 72 yr, their weights from 54 to 70 kg, and clinical examinations showed no abnormalities of their cardiorespiratory systems. Only subjects with normal body habitus were asked to participate. Nineteen patients consented to be studied.

Patients were premedicated with pethidine 50–100 mg and atropine 0.5 mg i.m. 60 min before, or with trimeprazine tartrate 50–60 mg by mouth 90 min before, the induction of anaesthesia. Anaesthesia was induced with 2.5% thiopentone 4 mg kg^{-1} and tracheal intubation was facilitated with suxamethonium 1 mg kg^{-1}. Anaesthesia was maintained with 1–2.5% halothane in oxygen through a Magill semi-closed breathing system. Within 10–15 min the inspired halothane concentration could be decreased to 0.5–1%, and once arterial pressure (AP), heart rate, and spontaneous rate of ventilation were stable, hexamethonium 0.5–1 mg kg^{-1} was administered. The exact dose was chosen by the anaesthetist on the basis of the patient's age and weight, the older patients receiving the smaller doses since the hypotensive effects of this drug are

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known to increase with age [7]. Lead II of the electrocardiogram was recorded simultaneously with the measurements of blood flow, from which it was ascertained that sinus rhythm prevailed during the study period. Two patients whose arterial pressure, heart rate, and ventilatory rates had not stabilized within 15 min after induction of anaesthesia were withdrawn from the study. Hand blood flow (HBF), forearm blood flow (FBF), systolic arterial pressure, heart rate and ventilatory rate were recorded before the administration of hexamethonium, and 9 and 18 min after hexamethonium had been given.

The subjects lay supine on a comfortable stretcher. The room temperatures varied from 23 to 25 °C on different days, but for each patient it was maintained within a range of 1 °C during the study period. Both upper limbs were slightly abducted and supported at sternal level. Systolic arterial pressure was monitored by recording the highest occluding pressure at which blood flow could be detected by the strain gauge in the forearm—a technique described by Mason and Braunwald [8].

The accuracy of this method was verified by comparing those pressures with direct intra-arterial pressures in six patients scheduled to undergo anaesthesia but not included in the study. In the latter group, the standard arterial pressure cuff was placed on the forearm and connected to a Statham P23 pressure transducer, the cannula in the radial artery of the same limb (which had been placed for clinical monitoring) was connected to another Statham P23 pressure transducer, and the mercury-in-rubber strain gauge was placed over the middle one-third of the forearm. The output from these three devices was registered on a four-channel recorder (Cardiac Recorders Ltd, London). The differences in systolic arterial pressure obtained between the two techniques for 64 comparisons averaged 1.53 ± 0.73 mm Hg in the range 30–107 mm Hg, being 8 mm Hg at the top end of the scale.

The FBF was measured by a mercury-in-rubber strain gauge [9] in the following manner [10]: The strain gauge measured the change in girth of the mid-forearm produced by periods of venous occlusion after the circulation to the hand had been excluded for 1 min (the change in girth is equated with change in volume of the forearm). HBF was measured by water plethysmography—as described previously [11]. The output from both plethysmographs was recorded on a multichannel recorder (Cardiac Recorders Ltd). FBF was measured in one arm while HBF was measured simultaneously in the other arm over 2 min in each of three different stages of the study: during anaesthesia alone, and at 8–10 and 17–19 min after the administration of hexamethonium. Measurements for each interval for each patient were averaged and those averages were combined with averages for other patients. The averaged measurements over each 2-min interval were recorded as the control, 9-min, and 18-min values. The systolic arterial pressure was determined before and after the measurements of the blood flows. The arterial pressure in the arm in which the HBF was being measured was also monitored by the Riva-Rocci method. The mean arterial pressure (MAP) was calculated by adding one-third of the pulse pressure to the diastolic pressure. Direct arterial cannulation was avoided because it might have affected the blood flow being measured. Pa_{CO_2} and Pa_{O_2} were measured at the end of the 18-min study in patients 3, 9, 12 and 15. This represented an attempt to sample Pa_{CO_2} and Pa_{O_2} of proportionally spaced patients throughout the study in order to approximate a representation of all patients studied.

Statistical evaluation was performed using the Student's *t* test and the Pearson correlation coefficients.

RESULTS

The effects of the administration of hexamethonium in patients anaesthetized with halothane can be seen in table I and figure 1.

The diastolic arterial pressure measured by the Riva-Rocci method was unclear in nine readings during the first hypotensive measurement and in 12 readings during the second measurement; for this reason, we used mainly the systolic arterial pressure measured by the strain gauge to assess changes, and to establish relationships with the respective blood flows.

From control, systolic arterial pressure had decreased by 33% at 9 min and 34% at 18 min; both changes were significant ($P < 0.001$). The MAP, which could be calculated in only 13 hypotensive measurements, had decreased by 26% and 30% by the 9-min ($P < 0.001$) and 18-min ($P < 0.001$) measurements, respectively. There was a 27% decrease in HBF 9 min after the administration of the hexamethonium, and that decrease was significant ($P < 0.001$); at 18 min,

TABLE I. *Effect (mean±SEM and range) of hexamethonium 0.5–1.0 mg* kg^{-1} *on arterial pressures and hand and forearm blood flows. Significant changes from control:* $*P < 0.05$; $***P < 0.001$. *AP = Arterial pressure; HBF = hand blood flow; FBF = forearm blood flow; MAP = diastolic AP+1/3 pulse pressure; HR = heart rate; f = rate of ventilation. Numbers in parentheses indicate the numbers of patients in whom variable was measured at each interval*

	Control	9 min after hexamethonium	18 min after hexamethonium
Systolic AP (mm Hg)	97.6±3.0 (17) 115–80	65.4±0.2*** (17) 95–50	67.5±4.0*** (8) 90–60
HBF (ml dl^{-1} min^{-1})	26.2±3.2 (17) 64–13	19.0±2.2*** (17) 39–9	22.0±2.5 (8) 30–11
FBF (ml dl^{-1} min^{-1})	4.3±0.3 (17) 7.1–2.4	3.1±0.2*** (17) 4.5–1.8	3.4±0.3* (8) 4.6–2.2
MAP (mm Hg)	74.2±3.4 (12) 93.3–56.7	54.7±2.7*** (8) 65–40	52.3±4.9*** (5) 70–40
HR (beat min^{-1})	74.9±3.5 (17) 100–48	80.9±3.1*** (17) 100–54	81.4±4.6 (8) 96–61
f (b.p.m.)	18.3±1.1 (12) 24–15	18.2±2.0 (12) 25–14	17.0±1.2 (8) 20–15

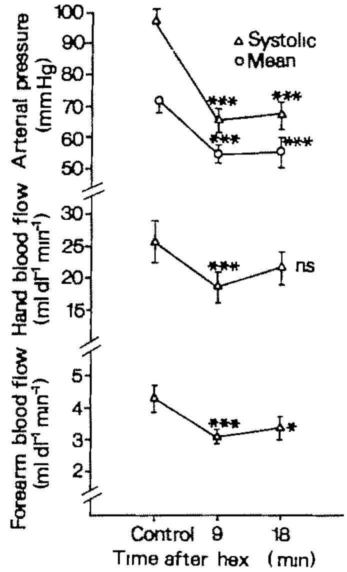

FIG. 1. Effect of hexamethonium (hex.) 0.5–1.0 mg kg^{-1}, on arterial pressure, and hand and forearm blood flows. Bars = SEM. Changes from control: $*P < 0.05$; $***P < 0.001$; ns = not significant.

the decrease was only 15% (ns). Five of the eight patients showed higher flows than those measured 9 min earlier and three of these values surpassed the control flow values. Statistically, the control and 18-min hand blood flows were not different. FBF had decreased 25% below control ($P <$ 0.001) at 9 min and 14% below control ($P = 0.02$) at 18 min. At this time, unlike the HBF, FBF continued to decrease or remained at the 9-min level in six of the eight patients. Sinus rhythm was present in all patients, and by the 9-min and 18-min measurements, the heart rate had increased 9% from control. This increase had occurred in 13 of the 18 patients by the 9-min measurement, being statistically significant ($P < 0.01$), but by 18-min it was present in only five of the eight patients ($P > 0.15$). The increase in heart rate was prevalent among patients who had a control rate lower than 80 beat min^{-1} at the 9-min period; the most common increase was 5 beat min^{-1}; one patient had an increase in heart rate of 26 beat min^{-1}, and three had an increase of 15 beat min^{-1}. Nine minutes later the heart rate had varied ±2 beat min^{-1} in six of the eight patients, had decreased by 6 beat min^{-1} in one patient, and increased by 6 beat min^{-1} in another patient.

The ventilatory rate had not changed significantly ($P > 0.05$) from control by either the 9-min or the 18-min measurement.

During the control period of halothane anaesthesia, there was significant correlation between systolic arterial pressure and HBF ($r = 0.69$ and $P = 0.0022$). MAP and HBF had a similar relationship ($r = 0.74$ and $P = 0.0058$). There was no correlation between age and HBF ($P = 0.92$) after correction for systolic arterial pressure or MAP had been made. FBF did not correlate with age, systolic AP or MAP ($P > 0.90$).

During hypotension, systolic arterial pressure and HBF changed in the same direction, but there was no correlation between them at either the 9-min ($r = 0.33$ and $P = 0.196$) or the 18-min ($r = 0.66$ and $P = 0.072$) observations. A similar lack of correlation was seen between systolic arterial pressure and FBF (highest $r = 0.35$). There was no correlation between the increase in heart rate and the changes in HBF ($r = -0.32$) or FBF ($r = -0.33$). MAP and age also lacked correlation with the hypotensive blood flows.

The magnitude of the change (Δ) in HBF at 9 min correlated positively with the magnitude of change in systolic arterial pressure ($r = 0.70$ and $P = 0.0018$); however, by 18 min this relationship was no longer statistically significant ($r = 0.50$ and $P = 0.21$). Also, ΔFBF correlated positively with the change in systolic arterial pressure at 9 min ($r = 0.59$ and $P = 0.013$). Again, as was the case with HBF, by the second hypotensive measurement there was no statistical correlation between ΔFBF and Δsystolic arterial pressure ($r = 0.14$). Lastly, the ΔFBF correlated negatively and indirectly with the baseline FBF ($r = 0.73$ and $P = 0.014$); that is, the higher the baseline FBF the less the decrease in FBF produced by decreasing systolic arterial pressure.

The average Pa_{CO_2} and Pa_{O_2} measured in four patients after the 18-min observation were 6.67±0.08 kPa and 26.9±0.32 kPa, respectively.

DISCUSSION

These findings show that the hypotension produced by small doses of hexamethonium in patients lightly anaesthetized with halothane temporarily decreases hand and forearm blood flows significantly. When analyses of the individual changes in blood flow rather than averages were evaluated, three of eight measured HBF were greater than the control flows 18 min after the administration of hexamethonium and six of the eight were higher than the 9-min flows. Thus it would appear that the recovery of HBF was genuine. The recovery of FBF was more elusive: while 15 of the 17 FBF values were lower than the control flows at 9 min, seven of the eights flows were lower than the control flows at 18 min and one had not changed. However, comparing the FBF measured at the 9-min and 18-min periods, three of the eight had increased minimally, two had not changed, and two had decreased minimally. Thus it seems that blood flow to the forearm muscle is affected for a longer period than blood flow to the hand. However, previously, Pauca and Hopkins [11] had observed in 11 unpremedicated patients under halothane anaesthesia that FBF decreased as time elapsed; in that study, after 4 min of halothane–oxygen anaesthesia, the FBF had decreased from the control value of 4.9 to 4.4 ml/100 ml of tissue, and at 10 min it was 2.8 ml/100 ml of tissue. This is in agreement with findings by Akester and Brody [12] and Eger and colleagues [13]. It is possible, therefore, that the persistent decrease in FBF in the present study was related to the decreasing effect of halothane on muscle blood flow.

Data presented by Davison [6] show that FBF decreased markedly in patients anaesthetized with halothane, placed in a 10° head-up tilt, paralysed with tubocurarine, hyperventilated, and treated with hexamethonium in doses similar to those used in our study. Davison did not study HBF and his observations differed from ours in at least two ways: he used a head-up position, and that position is known to decrease FBF in awake man [14]—the head tilt could also have decreased cardiac output caused by venodilatation in patients anaesthetized and given hexamethonium [15]— and he inflated the lungs artificially, and inflation of the lung through low-threshold pulmonary stretch receptors is known to increase limb blood flow in some species and to decrease it in others, although Shepherd [14] found it produced no effect in patients studied while on cardiopulmonary bypass. We preserved the neutral supine position and spontaneous ventilation, but could not avoid hypercapnoea, as confirmed in four of the eight patients studied for 18 min.

Kontos, Richardson and Patterson [16] measured FBF by venous occlusion plethysmography in 10 healthy men whose Pa_{CO_2} was increased to between 6.4 and 7.0 kPa; since inhalation of carbon dioxide did not change FBF, we assumed that hypercarbia did not affect FBF in our patients. Conversely, Xanalatos and co-workers [17] studied the effect of the inhalation of 5% carbon dioxide in a similar group of subjects and found that it decreased muscle blood flow significantly ($P < 0.05$). However, this finding does not contradict the results of Kontos' study because Xanalatos measured muscle blood flow by the clearance of xenon-133 from the tibialis anterior muscle, and that method detects only nutritional blood flow to muscle, while plethysmography measures total blood flow to the segment under observation. We have to assume that Davison [6] found a larger decrease in FBF than we did, and the difference could be attributed to the addition of lung inflation and a head-up position to halothane anaesthesia [11–13].

Therefore, it seems that muscle blood flow during hexamethonium-induced hypotensive anaesthesia is determined by the anaesthetic in use. Because isoflurane anaesthesia increases muscle blood flow by 200% [18] its combination with hexamethonium might have been a powerful way to produce controlled hypotension had not hexamethonium been removed from clinical use before the advent of isoflurane. In contrast to our findings with hexamethonium, Mason and Braunwald [19] found that nitroglycerine 0.6–0.9 mg given sublingually produced an 88% increase in FBF in 11 awake normal men and, in anaesthetized dogs, Wang, Liu and Katz [20] found that the intra-arterial injection of nitroprusside 5–20 μg increased femoral blood flow transiently up to 200%, and trimetaphan 5–10 μg increased femoral blood flow up to 300%. It seems that most other drugs used to produce hypotension during general anaesthesia increase muscle blood flow. This makes them much more powerful than hexamethonium, since muscle mass constitutes about 40% of body weight in man [21], and any increase in muscle blood flow could divert a large portion of the cardiac output, proportionally reducing the arterial pressure.

Although we did not measure cardiac output, we could assume that we had produced predominantly peripheral effects because we gave our patients only small doses of hexamethonium. Zimmerman, Brody and Beck [22] found, in 18 dogs, that small doses of hexamethonium (0.075–0.5 mg kg^{-1}) produced no depression of the sympathetic ganglia to the heart, only vasomotor depression. The small increase in heart rate and the lack of correlation between the changes in heart rate and those in HBF or FBF seen in our patients would also indicate that the changes were insufficient to alter the cardiac output.

Although we could not observe all 17 patients for 18 min, the information gathered from the eight we did observe at the end of that length of time indicated that, once hypotension had been established, the variables observed changed only minimally between the 9-min and the 18-min period. Because the change between the two intervals was so minimal, we made the assumption that there was no significant change throughout.

Fox, Goldsmith and Kidd [23] determined that the vasomotor control of skin blood flow in awake man is dominated either by vasoconstrictor tone (as in the hand, pinna of the ear, lips and nose, where temporary ablation of vasoconstrictor tone will increase blood flow) or by an active vasodilator mechanism (as in the forearm, scalp, forehead, chin, submandibular area, neck and upper chest). Halothane, like most anaesthetics, increases blood flow to the skin of the hand [21] and the vasoconstrictor tone returns only with awakening from anaesthesia [11]. Pauca and Hopkins [11] found that HBF did not change in patients anaesthetized with halothane when the temperature of the water in the plethysmograph was changed from 34 °C to 24 °C but, when the patients awakened, the HBF decreased from a mean of 26.2 ml dl^{-1} to a mean of 0.2 ml dl^{-1}. Thus, the study of the HBF is of interest, not as a reflection of the state of the skin circulation in general, but as an index of vasoconstrictor response. Because halothane anaesthesia increased the HBF by 496% [11], we could assume that this represents maximal vasodilatation and that the peripheral vasodilatory effect of hexamethonium would not increase HBF any further. However, even though, during halothane anaesthesia, the HBF is proportional to systolic arterial pressure, when hexamethonium is added in low doses, the HBF no longer correlates with systolic arterial pressure ranging from 95 to 50 mm Hg.

Some correlations in this study provide interesting insights to the factors influencing peripheral blood flow: (a) Under halothane anaesthesia the HBF is dependent on arterial pressure ($r = 0.69$ and $P = 0.0022$), while the FBF is not; (b) the complete lack of correlation between systolic arterial pressure and the hand and forearm blood flows after hypotension is established during anaesthesia indicates that, under these conditions, limb blood flows are independent of systolic arterial pressure in the range 95–50 mm Hg; (c) the direct correlation between ΔAP and ΔHBF and ΔFBF indicates that a large decrease in systolic arterial pressure will produce a similar decrease in peripheral blood flow, although such a change is only of short duration; and (d) the negative correlation between ΔFBF and baseline FBF could indicate that, the higher the initial state of muscle perfusion, the less effective hypotension will be in reducing muscle blood flow.

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EFFECT OF SUXAMETHONIUM ON THE ICP OF CATS WITH AND WITHOUT THIOPENTONE PRETREATMENT

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SUMMARY

Twelve cats were assigned equally to two groups, one with normal, and the other with artificially-increased intracranial pressure. When suxamethonium was administered to these animals, the intracranial pressure increased in both groups, irrespective of their baseline intracranial pressure. When the same dose of suxamethonium was administered after pretreatment with thiopentone in both groups of animals, the intracranial pressure again increased from the control values.

The effect of suxamethonium on the intracranial pressure (ICP) is controversial. Some investigators have shown that suxamethonium increases intracranial pressure [1–3], while others claim that it has no significant effect [4]. Barbiturates decrease ICP by constricting cerebral blood vessels; however, brain tissue oxygenation is not compromised because coupling between metabolism and flow is maintained [5]. This study was designed to ascertain whether suxamethonium increases ICP and to determine the effectiveness of barbiturate pretreatment in attenuating this change.

MATERIALS AND METHODS

Twelve cats (2.5–3.5 kg) were anaesthetized with isoflurane, the trachea was intubated using a tube lubricated with amethocaine ointment and the lungs ventilated with a Harvard animal respirator. Femoral vessels were cannulated to permit drug administration, monitoring of arterial pressure (AP) and blood-gas analysis. The cats were placed in the sphinx position using a stereotactic frame with the interaural plane 127 mm above the level of the chest. The scalp and the underlying muscles were dissected and a 5 mm hole trephined in the left parietal area. A 7-French gauge catheter was inserted to the subarachnoid space and connected to a pressure transducer to allow the continuous monitoring of ICP. Six cats were allocated to each of two groups. In one group, normal ICP (N-ICP) was maintained. In the other group, a 5-mm hole was trephined in the right parietal area and a 10-French gauge Foley catheter was placed in the extradural space. Inflation of the balloon artificially increased ICP (AI-ICP). All trephined holes were made airtight with bone wax.

Upon completion of the preparation, the operative sites were infiltrated with 0.5 % bupivacaine 2–3 ml. Anaesthesia was maintained with nitrous oxide in 30 % oxygen and 0.5 % isoflurane. In one group (AI-ICP) the Foley catheter was inflated slowly with incremental volumes (0.1–0.2 ml) of water at 5-min intervals until the ICP reached 30 mm Hg and remained constant. Mean arterial pressure, heart rate (HR), ICP, ECG and end-tidal carbon dioxide concentration were monitored continuously using a Beckman R 612 (eight-channel) physiological recorder. Arterial-blood gas tensional were analysed (Corning 168 pH/gas analysers) frequently and Pa_{CO_2} was maintained at 30 ± 2 mm Hg (normocarbia for cats 28–32 mm Hg) [6]; Pa_{O_2} was maintained slightly greater than 100 mm Hg, pH at 7.35 ± 0.5. Rectal and brain temperatures were maintained at 37 ± 0.5 °C. Lactated Ringer's solution was infused (5 ml kg^{-1} h^{-1}) to replace insensible fluid loss during the procedure.

After vital signs had remained stable for 1 h, the arterial pressure, ECG and the ICP were recorded before and during the administration of 2 %

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suxamethonium 2 mg kg^{-1} to all aminals. Forty-five minutes later, thiopentone 15 mg kg^{-1} (sleep dose for cats) was administered, followed by suxamethonium 2 mg kg^{-1}. All measurements were repeated. Following a 45-min period of stabilization, only thiopentone 15 mg kg^{-1} was administered. In order to evaluate the effect of fluid volume on ICP and arterial pressure in both groups of animals, volumes of saline (0.3 ml ± 0.2) equal to the volume of suxamethonium were administered. All measurements were taken at end-expiration. The zero value for ICP was referenced at the external auditory meatus. Control values of mean arterial pressure, HR, and ICP were compared with the values obtained during drug administration and analysed by the Student's paired *t* test. *P* values less than 0.05 were considered significant.

RESULTS

The results are summarized in table I and in figures 1 and 2.

Suxamethonium increased ICP significantly from 7±1 to 10±2 mm Hg (mean ± SD) ($P < 0.05$) in cats with N-ICP and from 28±0.6 to 36±1 mm Hg ($P < 0.05$) in the AI-ICP group. Thiopentone pretreatment resulted in an initial decrease in ICP followed by a significant increase in ICP in both groups; in the N-ICP group ICP increased from 8±0.8 to 12±1 mm Hg ($P < 0.05$) and in the AI-ICP group from 28±0.4 to 35±4 mm Hg ($P < 0.05$).

The increase in arterial pressure was not significant in the group treated with suxamethonium alone. Arterial pressure decreased significantly with thiopentone alone and when pretreated with thiopentone. Heart rate increased from 157±6 to 163±21 (N-ICP) and from 154±4 to 170±18 (AI-ICP) beat min^{-1} in the two groups after suxamethonium; the changes were not significant. Following thiopentone pretreatment, HR increased from 159±7 to 192±16 (N-ICP) and 160±7 to 170±10 (AI-ICP) beat min^{-1} (ns). Thiopentone administered alone increased the HR from 153±9 to 171±15 (N-ICP) and 151±5 to 173±17 (AI-ICP) beat min^{-1}.

Intracranial pressure, HR and arterial pressure did not change when volumes of saline equal to the corresponding volumes of suxamethonium were administered.

The control arterial pressures and HR in both groups were not significantly different. Thiopentone, however, was associated with a consistent decrease in arterial pressure and ICP in both groups.

DISCUSSION

Reports on the effect of suxamethonium on ICP are contradictory. In animals with intracranial hypertension [7] and in dogs [1], no change in ICP was shown with suxamethonium, whereas an increase in ICP has been found in cats [2]. In man, suxamethonium caused a delayed increase in ICP when monitored supratentorially [3]. Another study reported the average increase in ICP measured supratentorially to be 5 mm Hg; however, in one patient the increase was + 18 mm Hg [8]. Lam, Nicholas and Manninen [4] measured lumbar subarachnoid pressure of patients with minimal intracranial hypertension (< 15 mm Hg) who were deeply anaesthetized via a face-mask. These patients were not monitored for end-tidal carbon dioxide concentration and demonstrated no change in ICP [4]. Marx,

TABLE I. *Effect of suxamethonium, suxamethonium after pretreatment with thiopentone and thiopentone alone on mean ICP (mm Hg), mean AP (mm Hg) and heart rate (HR) (beat min^{-1}). All values expressed as ±1SD.* *P < *0.05*

	Normal ICP group (n = 6)			Increased ICP group (n = 6)		
	AP	ICP	HR	AP	ICP	HR
Control	122±7	7±1	157±6	114±7	28±0.6	154±4
Suxamethonium	124±6	10±2*	163±21	122±10	36±1*	170±18
Control	120±4	8±0.8	159±7	115±4	28±0.4	160±7
Thiopentone/ suxamethonium	101±1*	12±1*	192±16	96±6	35±4*	170±10
Control	125±5	7.5±2	153±9	120±6	29.8±3	151±5
Thiopentone	92±4*	5±1.55	171±15	85±4	23±2.8*	173±17

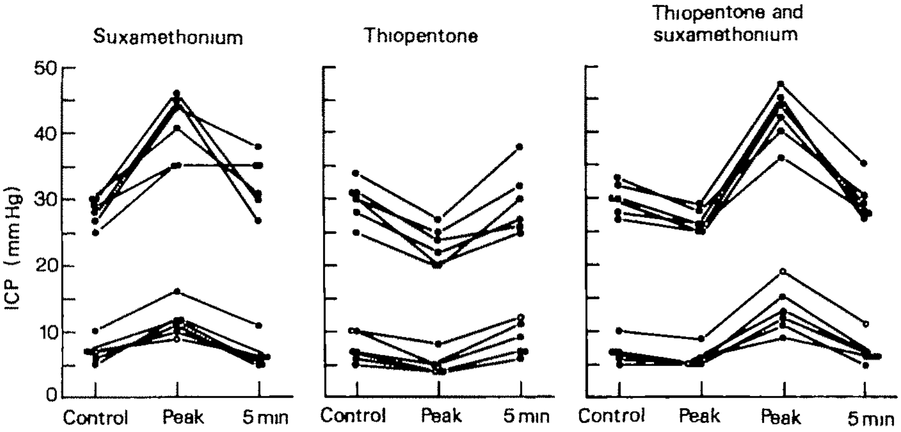

FIG. 1. This figure represents the effect of suxamethonium, thiopentone, and thiopentone and suxamethonium combined, on the normal ICP (○ : lower groups of traces) and increased ICP (● : upper groups of traces) of cats.

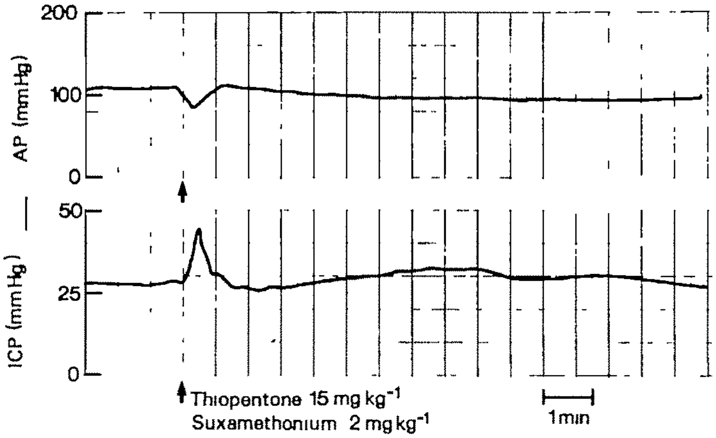

FIG. 2. Typical response to thiopentone and suxamethonium on the ICP and AP of a cat with intracranial hypertension. Note the biphasic effect on ICP

Andrew and Orkin [9] and Sondergard [10] reported increases in ICP using the same route for measurement.

Several differences are evident in the design of the above experiments: design, species, route of ICP monitoring, method of suxamethonium administration, magnitude of intracranial hypertension, extent of autoregulatory impairment and the concurrent haemodynamic changes associated with laryngoscopy and intubation.

The use of the lumbar route to measure ICP may not truly reflect pressure changes in the supratentorial compartment. Acute changes in pressure or volume in the supratentorial compartment tend to compress and block the communicating channels with the infratentorial cisternal and lumbar areas. One study describes the effect of suxamethonium in cats with intracranial hypertension; the ICP, however, was measured via the infratentorial cisternal route in a model with hydrocephalus [12].

In our cats, we utilized a space occupying lesion (a clinically relevant model) to increase ICP which was then monitored via the supratentorial subarachnoid route. Suxamethonium was administered as a bolus. The arterial carbon dioxide tension, arterial pressure and temperature were continuously monitored and maintained within the physiological range. During this period, all manipulations that might increase cerebrovascular haemodynamics were avoided (laryngoscopy, tracheal intubation or transtracheal spray of local anaesthesia).

Our results confirm that bolus administration of suxamethonium significantly increased ICP of cats with normal and with increased ICP. However, the increase in the normal ICP group was within the normal range and, therefore, not significant clinically.

Pretreatment with thiopentone did not prevent the increase in the ICP in either group. The immediate response to thiopentone was decrease in ICP but, when followed by suxamethonium administration, the ICP increased beyond the control value.

The reason why suxamethonium increases ICP is unknown. Muscle fasciculations increase venous return and hence cardiac output which in turn may increase ICP [1]. An increase in blood noradrenaline concentration during suxamethonium administration has been observed recently and implicated as the cause of haemodynamic hyperactivity [11]. Noradrenaline would increase the arterial pressure and a non-autoregulating animal should experience increased ICP. We did not observe this parallel increase when thiopentone was administered in combination with suxamethonium. In our experiments thiopentone decreased arterial pressure; nonetheless, ICP increased as arterial pressure decreased (fig. 2). Accordingly, generalized haemodynamic hyperactivity does not appear to be the cause for the ICP increase. Other investigators have suggested that the increased brain activity with suxamethonium, as demonstrated by EEG, was related to neuronal discharge from muscle spindles. The increased neural activity in turn led to increased cerebral blood flow and thus increased ICP [3, 12].

Obviously, increases in the ICP of patients with existing intracranial hypertension will compromise cerebral blood flow and may even lead to herniation of brain tissue. Although observations in animal experiments should not be extrapolated to humans, there is increasing evidence that suxamethonium should be used with caution in patients with intracranial hypertension. Precurarization before the administration of suxamethonium or the selection of a short-acting non-depolarizing relaxant are suggested alternatives [3, 13, 14].

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RATE OF INDUCTION OF HYPOTENSION WITH TRIMETAPHAN MODIFIES THE INTRACRANIAL PRESSURE RESPONSE IN CATS

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SUMMARY

An infusion of 0.1% trimetaphan was administered to eight cats with artificially increased intracranial pressure (ICP) in order to decrease their mean arterial pressure (MAP) from 121 ± 9.5 (SEM) to 58 ± 4.6 mm Hg in less than 1 min. All cats developed an increase in intracranial pressure (ICP) (from 16 ± 1.4 to 23 ± 3.2 mm Hg) accompanied by a partial rebound in MAP. Eight additional cats received 0.1% trimetaphan to decrease their MAP from 128 ± 13.4 to 52 ± 8.1 mm Hg over more than 2 min. Four of these cats followed the same pattern, with ICP increases from 19 ± 1.1 to 31 ± 3.9 mm Hg, while in the other four ICP did not change. In nine of the 12 cats with an ICP increase, that increase was initiated before the partial MAP rebound. We conclude that trimetaphan causes clinically significant ICP increases in cats with increased ICP, that partial rebound in MAP frequently exacerbates these increases in ICP, and that rapid induction of hypotension tends to increase the frequency with which trimetaphan increases ICP.

In 1954 Schallek and Walz [1] noted, in dogs, that the more rapidly hypotension was induced with trimetaphan, the more the EEG was depressed. Stullken and Sokoll [2] made the complementary finding that trimetaphan caused significant increases in the intracranial pressure (ICP) in cats. Conversely, Turner and colleagues [3] found a clinically significant increase in ICP in only two of 21 patients to whom trimetaphan was given to induce hypotension. As a result, there was no statistically significant mean increase for the group and the authors suggested that TMP does not increase ICP.

Marsh and colleagues [4] reported that the technique by which nitroprusside is administered modified the ICP response in cats. This led us to wonder if different techniques of administration would cause different ICP responses to trimetaphan-induced hypotension also. If so, previously observed individual variability could be accounted for, and contradictory conclusions reconciled.

To investigate the effect of technique of administration on ICP, we induced hypotension with trimetaphan in cats with induced intracranial hypertension using two different infusion rates.

MATERIALS AND METHODS

After institutional review board approval for animal use had been received, 16 male mongrel cats were anaesthetized with pentobarbitone 32.5 mg kg^{-1} i.p., with 32.5-mg s.c. supplements as needed to prevent movement. The cat was placed in the supine position, the trachea intubated and the lungs ventilated with 30% oxygen in nitrous oxide. Physiological saline and drugs were infused via the cephalic vein, and arterial pressure monitored via a catheter in a femoral artery. Intracranial pressure was monitored, and adjusted through a 19-gauge needle placed in the cisterna magna and connected by a T-fitting to a bag of physiological saline (corrected to the pH of the cerebrospinal fluid) and to a transducer [5] (fig. 1). Fluid was added to, or withdrawn from, the intracranial space to achieve

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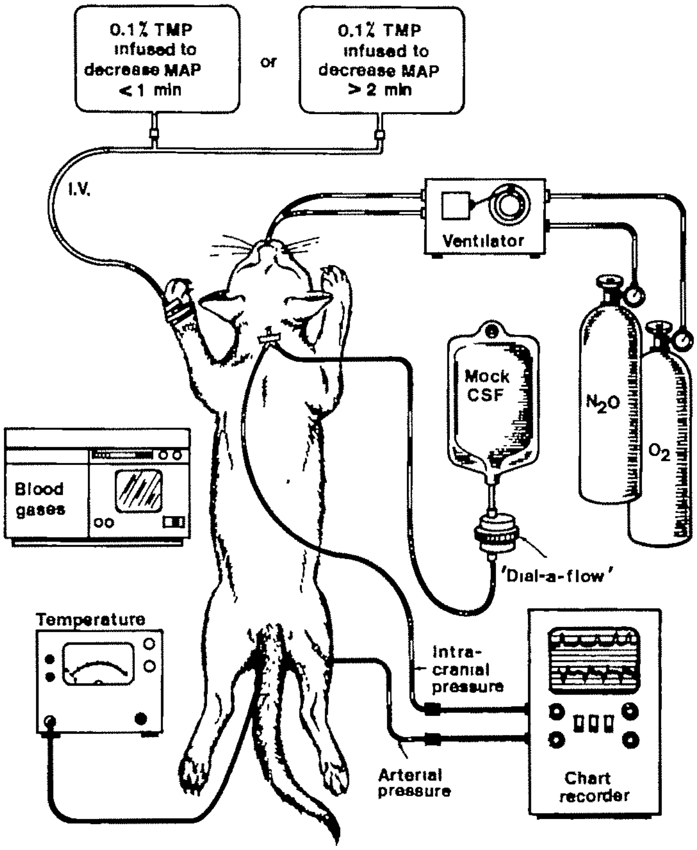

FIG. 1. Schematic representation of lay-out of experiment and of variables monitored.

the desired baseline ICP. Needle placement was considered correct when the ICP fluctuated with ventilation.

A rectal probe was placed to monitor temperature. Arterial blood-gas tensions and pH were measured: in all experiments pH was 7.35 ± 0.03; Pa_{O_2} was greater than 10.7 kPa; Pa_{CO_2} was 4.7 ± 0.3 kPa; and temperature was 37 ± 1.5 °C.

Mean arterial pressure (MAP) was calculated as the diastolic pressure plus one-third of the pulse pressure. An infusion of 0.1 % trimetaphan (Arfonad) in 5 % dextrose in water was titrated at one of two rates in order to decrease MAP to approximately 55 mm Hg. A "rapid" rate of induction of hypotension ($n = 8$) decreased MAP to a minimum in less than 1 min. A "slow" rate of induction ($n = 8$) brought the MAP to a minimum over more than 2 min. At least 30 min passed between any pentobarbitone administration and an infusion of trimetaphan, and ICP was increased for 30–60 min before each administration of trimetaphan.

All of the eight cats receiving the rapid induction experienced a partial rebound of arterial pressure during the infusion, as did four of the cats receiving the slow induction. For all cats in each treatment group, and for the subset of cats without a rebound in arterial pressure in the slow induction group, MAP, ICP and heart rate (HR) at maximum achieved hypotension were compared with control values by paired two-tail *t* tests. In the cats in which there was a rebound of arterial pressure, values at maximum hypotension and maximum rebound were compared with control values by paired two-tail *t* tests if a one-way ANOVA for repeated measures proved significant at $P < 0.05$.

RESULTS

The results are summarized in table I.

When hypotension was induced rapidly with a 0.1 % solution of trimetaphan, such that MAP decreased to 58 ± 4.6 mm Hg in less than 1 min,

TABLE I. *Effects of rapid* v. *slow induction of hypotension with 0.1 % trimetaphan on mean arterial pressure (MAP) (mm Hg), intracranial pressure (ICP) (mm Hg) and heart rate (HR) (beat* min^{-1}*) (mean ± SEM).* *P < *0.05 compared with control*

	All		With rebound during infusion			Without rebound	
	Control	Hypotension	Control	Hypotension	Rebound	Control	Hypotension
Fast technique							
n	8		8			0	
MAP	121±9.5	58±4.6*			102±6.4*		
ICP	16±1.4	17±6.0	(Same as "all")		23±3.2*		
HR	160±14.5	187±10.3*			223±9.2*		
Slow technique							
n	8		4			4	
MAP	128±13.4	52±8.1*	136±14.1	50±8.5*	112±12.7	119±14.5	56±8.8*
ICP	18±1.1	19±1.8	19±1.1	21±1.8	31±3.9*	16±0.4	17±0.7
HR	197±19.4	192±20.5	209±13.1	197±10.3	246±10.3	185±25.5	187±29.3

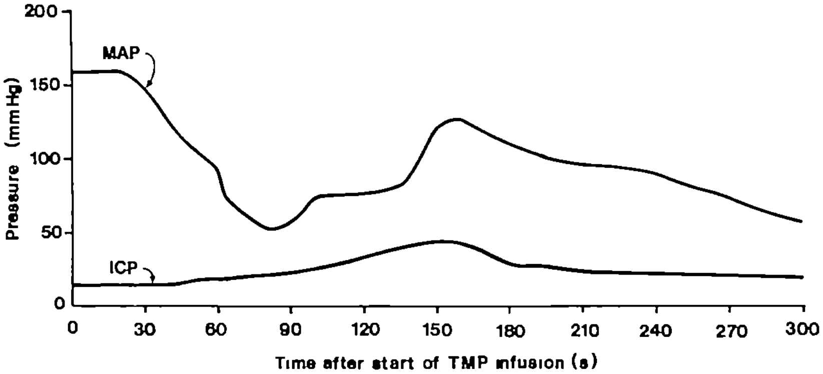

FIG. 2. Tracing from one study during which hypotension was induced rapidly.

this decrease was followed by a partial rebound of arterial pressure in all cats. The rebound was transient, occurred during the infusion, and was followed by a decrease approaching 55 mm Hg. Figure 2 shows a typical tracing. In each of these cats there was an increase in ICP, from a control mean of 16±1.14 to 23±3.2 mm Hg. The duration of the increase in ICP and the increase in in arterial pressure paralleled each other with a Pearson correlation coefficient between the two durations of 0.98 ($P < 0.001$). The average duration of the increase in ICP was 324±113 (SEM) s. The average duration of partial rebound in arterial pressure was 301±97 s. Despite the close relation of the durations of the increases in arterial pressure and ICP, the increase in ICP preceded the increase in arterial pressure in six cats.

When hypotension was induced more slowly the results were more variable. Induction of hypotension was smooth in four of eight cats, with MAP decreasing from 119±14.5 to 56±8.8 mm Hg and ICP remaining essentially unchanged at 17 mm Hg. The other four cats receiving the slow induction followed the same pattern as the cats which received the rapid induction. That is, during the infusion of the trimetaphan MAP decreased initially from 136±14.1 to 50±8.5 mm Hg. Shortly thereafter, but still during the infusion, MAP rebounded to 112±12.7 and then returned to about 50 mm Hg. The ICP increased roughly in parallel, from 21±1.8 to 31±3.9 mm Hg. As the MAP returned toward 50 mm Hg the ICP also decreased toward 17 mm Hg. In three of these four cats the ICP started to increase before the arterial pressure increased. The duration of the rebound in arterial pressure was 121±24 s. The duration of the rebound in ICP was 122±28 s. The Pearson correlation coefficient for the duration of rebound in arterial pressure and the duration of the increase in ICP was 0.92 ($P < 0.0001$).

The association between the increase in ICP and the partial rebound in arterial pressure during infusion of trimetaphan was statistically significant ($P < 0.05$, Fisher Exact). In nine of the 12 cats in which ICP increased during the infusion of trimetaphan (six of eight from the fast group, three of four from the slower group), that increase began before the rebound. The association between the increase in ICP and initiation of change before partial rebound was also significant (cross-tabulation of increase *v.* no increase by prior *v.* not prior or no rebound, $P < 0.05$, Fisher Exact).

DISCUSSION

All eight cats in which hypotension was induced in less than 1 min had significant increases in ICP. Although the effect of the partial rebound in arterial pressure is implicated as a confounding variable, in six cats the increase in ICP began 20 s or more before the rebound in arterial pressure. The increase in ICP before the rebound in arterial pressure may be the result of either autoregulation or direct cerebral vasodilatation, that is, loss of autoregulation. If autoregulation were maintained, we would expect to see an increase in ICP as the cerebral vessels dilated in response to a decreased cerebral blood flow. On the other hand, if trimetaphan had a direct cerebrovascular dilating action which abolished autoregulation, ICP would also increase. If autoregulation remained intact, we should see a decrease in ICP during the rebound in arterial pressure after 0.5–2 min [6]. The fact that ICP remained increased for the entire duration of the rebound (about 5 min) argues that autoregulation was lost and that trimetaphan given to decrease arterial pressure in less than 1 min acts as a cerebrovascular dilator. These findings are in agreement with those of Stullken and Sokoll [2]. They also may corroborate the work by Ishikawa and co-workers [7] in dogs with normal ICP. Although they induced hypotension more slowly than we, they found that ICP doubled, from 6 to 12 mm Hg, within 5 min of starting the infusion of trimetaphan, and returned to control within 20 min.

There is other evidence that trimetaphan is a direct vasodilator. Siems and Rottstein [8] demonstrated, in dogs, that tetraethylammonium chloride (TEAC), the parent compound of trimetaphan, had a direct vasodilating action that was at least as important as its effects on the vasomotor nerves via ganglionic blockade. McCubbin and Page [9] found that the hypotensive action of trimetaphan in dogs was not decreased by section of the spinal cord at C6, removal of the paravertebral sympathetic chains, ganglionic blockade with TEAC or hexamethonium, or the administration of histamine, indicating that trimetaphan-induced hypotension in dogs is independent of sympathetic block or histamine release.

The action of trimetaphan on isolated cerebral arteries was examined by Harioka and associates [10], who showed that trimetaphan was a direct arterial vasodilator and alpha-adrenoceptor antagonist. However, the vasodilatation was more prominent in extracerebral arteries than in cerebral arteries. If this finding can be extended to intact animals, perhaps during slow induction of hypotension, this differential action is more prominent, with blood pooling extracerebrally; during more rapid induction a higher concentration of trimetaphan is delivered to the cerebral arteries, causing them to dilate more rapidly. Additionally, trimetaphan may increase intracranial blood volume by blocking sympathetic innervation of cerebral vessels [2].

Although an increase in arterial pressure can cause an increase in ICP when cerebral autoregulation is lost, we may, perhaps, differentiate the effect of trimetaphan on ICP from the effect of the rebound in arterial pressure by looking only at those cats which experienced an ICP increase before the rebound in arterial pressure. Although the rebound in arterial pressure was a common occurrence in our study, its cause was not clear. It is tempting to suppose that, in the observations in which a partial rebound followed an increase in ICP, the partial rebound occurred because of the ICP increase: that is, the rebound may have been a Cushing response. In man the Cushing response is inconsistent [11], but our experience in several other experiments using this model [5, 12–16] suggests that the Cushing response is more uniform in cats: on a few occasions during previous investigations we have inadvertently increased ICP rapidly and on most of those occasions arterial pressure has increased as if to maintain cerebral perfusion pressure. However, direct investigation of the Cushing response in cats is beyond the scope of the present paper.

A related question is whether acute increases in ICP itself, affect autoregulation. We have not investigated this, but others, using models similar to ours, have found no effect on autoregulation until ICP approaches MAP [17–19].

It should be pointed out that decreases in cerebral perfusion pressure (CPP = MAP − ICP) secondary to decreases in MAP can cause loss of autoregulation. In fact, loss of autoregulation caused by hypotension with normal ICP occurs at a higher CPP than does loss of autoregulation caused by increased ICP during normotension [18, 20]. However, as we noted earlier, loss of autoregulation during hypotension should not lead to increased ICP.

It is also true that brain ischaemia can cause increased ICP through cytotoxic oedema, followed by hyperaemia as the arterial pressure recovers, at times aggravated by vasogenic oedema if MAP increases rapidly to hypertensive values. However, oedema formation and resolution take considerably more time than did the onset and resolution of the increase in ICP in our cats. Accordingly, we think that oedema and hyperaemia secondary to ischaemia were not implicated in our results, and that our observations should be attributed to changes in cerebral blood volume.

Do our findings have clinical relevance? Turner and colleagues [3] reported that ICP was increased in 10% of their patients during trimetaphan-induced hypotension. Ten percent is a high rate of untoward reactions, but it appears to be much lower than the response found by Stullken and Sokoll [2] in cats. In fact, we cannot compare percentages because Stullken and Sokoll reported group averages, not individual responses. Turner and colleagues [3] suggested the difference between the two studies was attributable to a species difference in sympathetic control of cerebral vasomotor tone: "alterations in intracranial blood volume produced by sympathetic blockade are relatively much greater in the cat than in man, except when patients with critical intracranial compression are studied." However, only six of Turner and colleagues' trimetaphan group began with an ICP greater than 14 mm Hg. If we take these six as the clinically relevant sample of patients with critical intracranial compression, then two of six (33%) had significant increases in ICP; that is, as implied by Turner and colleagues [3], the response to trimetaphan of different species with initially increased ICP may not be so different. Also, all of the patients of Turner and colleagues [3] had a slow induction of hypotension and a steady reduced arterial pressure—the conditions which were least likely to cause an increase in ICP in our study.

Evidence in man [3] with intracranial hypertension and our evidence from cats with artificially increased baseline ICP suggest that trimetaphan can cause clinically significant increases in ICP when intracranial hypertension is present. Our results also suggest that the risk of this increase is reduced if hypotension is induced slowly.

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ANTERIOR FONTANELLE PRESSURE RESPONSES TO TRACHEAL INTUBATION IN THE AWAKE AND ANAESTHETIZED INFANT†

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SUMMARY

In order to define the changes in intracranial pressure which occur during tracheal intubation in young infants, a Ladd transducer was used to monitor anterior fontanelle pressure (AFP) non-invasively in awake (group 1, $n = 14$) and anaesthetized (group 2, $n = 10$) infants during intubation of the trachea. Heart rate and systolic arterial pressure were also recorded. In quiet, undisturbed infants, AFP (mean ± SEM) was similar in groups 1 (9.6 ± 0.5 mm Hg) and 2 (8.7 ± 0.8 mm Hg); with crying, AFP increased significantly in both groups. During laryngoscopy in group 1, AFP increased to 33.5 ± 3.6 mm Hg, which was significantly greater than in the quiet infant, but did not differ significantly from measurements in the crying infant. In group 2, AFP increased significantly to 15.8 ± 18 mm Hg during laryngoscopy. This increase was significantly less than the group 1 response. Neither heart rate nor systolic arterial pressure changed significantly in either group during laryngoscopy—when compared with measurements in the quiet state. It was concluded that AFP increases significantly during intubation and during crying in the infant. The response to intubation is only partially attenuated by the prior administration of general anaesthesia.

Rapid control of the airway is essential during the induction of anaesthesia in the small infant. Difficulty in ventilating by mask, and the discovery of unsuspected upper airway anomalies, may result in difficulty with tracheal intubation. As a result, some authorities [1,2] recommend that intubation be performed before the induction of anaesthesia.

Raju and colleagues [3] reported that intracranial pressure (ICP) increases during orotracheal intubation in the awake infant. Kelly and Finer [4] reported similar findings during nasotracheal intubation in the sick neonate. Hatch and Sumner [2] suggested that these increases in ICP in the premature neonate may result in intracranial haemorrhage. However, as yet, there has been no report of a study which compares ICP responses to tracheal intubation in the awake and anaesthetized infant.

The Ladd transducer is an accurate non-invasive monitor of neonatal anterior fontanelle pressure (AFP) [5] which correlates well with actual ICP [6]. This study was designed to compare the effects of tracheal intubation on AFP, measured with the Ladd transducer, in awake and anaesthetized infants.

PATIENTS AND METHODS

Following institutional approval, 24 infants were studied. Informed verbal consent was obtained from the parents. All infants were less than 8 weeks post-natal age, ASA I or II, and were scheduled to undergo a variety of surgical procedures. Those with central nervous system defects or neurological disease were excluded.

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Infants were fasted for 4 h and did not receive preoperative medication. On arrival in the operating room all infants were placed supine with the head in a neutral position supported by a head ring. The hair over the anterior fontanelle was shaved and the scalp painted with tincture of benzoin. A calibrated Ladd transducer was placed over the anterior fontanelle and secured by adhesive foam to minimize the effects of application pressure [6]. A single-channel chart recording of AFP was obtained throughout the procedure. Arterial pressure (by cuff), Doppler flow and the electrocardiograph were monitored. All patients were preoxygenated for 2 min. Infants who were awake during intubation of the trachea (group 1) were given atropine 0.02 mg kg^{-1} i.v. 2 min before intubation. In those patients anaesthetized before intubation (group 2), anaesthesia was induced with i.v. sodium thiopentone 5 mg kg^{-1}, atropine 0.02 mg kg^{-1} and suxamethonium 2 mg kg^{-1}. After a brief period of manual ventilation with 100 % oxygen, the trachea was intubated. In both groups, care was taken during intubation to ensure that no hyperextension or hyperflexion of the neck occurred. Extraneous pressure on the Ladd transducer was avoided. Anaesthesia was maintained with halothane or isoflurane supplemented with nitrous oxide in oxygen. Intermittent positive pressure ventilation was used in all infants with zero end-expiratory pressure. All infants were supine and horizontal throughout the study.

TABLE I. *Demographic data (mean ± SEM).* *$P < 0.05$

	Group 1	Group 2
Number of patients	14	10
Post-conceptual age (weeks)	41.4±1.0	43.2±1.1
Weight (kg)	3.2±0.2	3.9±0.2*

The AFP was recorded five times in each case; pre-induction in the quiet, undisturbed infant; pre-induction during crying; peak pressure during laryngoscopy; immediately after tracheal intubation; and during steady state general anaesthesia. Heart rate and arterial pressure were measured before induction, at intubation, and during steady state general anaesthesia. All measurements were made by the investigator who was not involved in anaesthetizing the infant.

The demographic data were compared using Student's unpaired t test. Within groups, statistical significance was determined by comparing values with quiet measurements using two-way analysis of variance and the Student–Newman–Keuls multiple range test. Values at each of the five recordings in both groups were compared using Student's unpaired t test. Statistical significance was accepted as $P < 0.05$. Data are presented as mean ± standard error of the mean.

RESULTS

Demographic data for groups 1 and 2 are shown in table I. Group 1 patients weighed less than group 2 patients, but they did not differ significantly in post-conceptual age.

Indications for surgery were: inguinal herniotomy ($n = 5$), pyloromyotomy ($n = 5$), creation of colostomy ($n = 3$), pyeloplasty ($n = 2$),

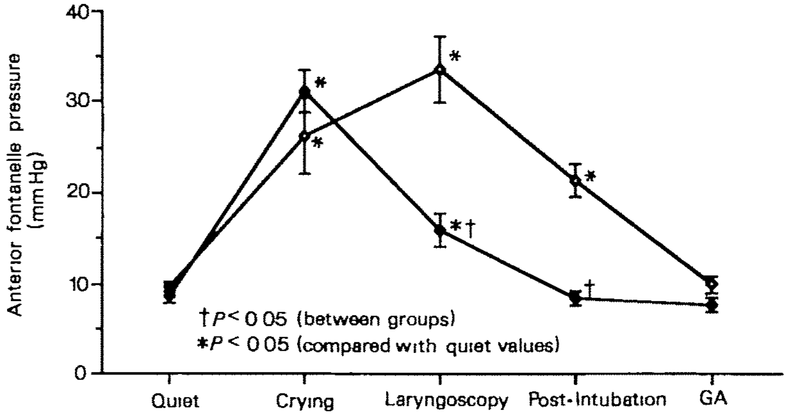

FIG. 1. Anterior fontanelle pressure responses (mean ± SEM) in infants awake (◇) or anaesthetized (◆) during intubation of the trachea.

TABLE II. *Changes in heart rate (HR) and systolic arterial pressure (SAP) (mean ± SEM) during intubation and induction of anaesthesia.* * $P < 0.05$ *compared with pre-induction*

	Group 1		Group 2	
	HR (beat min^{-1})	SAP (mm Hg)	HR (beat min^{-1})	SAP (mm Hg)
Pre-induction	173.2±7.8	94.4±4.5	173.2±8.0	92.5±3.5
Intubation	169.3±13.9	120.0±14.1	175.4±11.4	103.9±8.1
General anaesthesia	174.3±4.0	79.2±7.2	172.7±5.8	77.8*±5.3

insertion of central venous line ($n = 1$), gastrostomy ($n = 1$), vesicostomy ($n = 1$), removal of corneal sutures ($n = 1$), excision of sacral teratoma ($n = 1$), dilatation of choanal atresia ($n = 1$), cystoscopy ($n = 1$), laparotomy ($n = 1$) and ligation of patent ductus arteriosus ($n = 1$).

In both groups AFP increased significantly during crying compared with the quiet state. A significant increase also occurred during laryngoscopy in both anaesthetized and awake patients. In group 1, the increase in AFP associated with laryngoscopy did not differ significantly from that observed during crying. In group 2, however, the increase was significantly less than that seen with crying and was also significantly less than in group 1 infants (fig. 1). Changes in heart rate (HR) and systolic arterial pressure (SAP) are shown in table II. There was no significant difference in SAP or HR before induction. Values obtained during laryngoscopy, and during general anaesthesia, were also not significantly different except in group 2, in which SAP decreased significantly during anaesthesia. This was not felt to be clinically significant.

DISCUSSION

Significant increases in AFP during awake intubation in infants were demonstrated. The increases were significantly attenuated in infants anaesthetized before intubation. Although group 2 infants were slightly older, this difference was not statistically significant. Group 2 infants who were intubated asleep were significantly larger. As larger infants are generally more vigorous, they would be expected to have greater increases in AFP than smaller, weaker infants during airway manipulation. We feel, therefore, that the difference in weight does not invalidate our conclusions.

In another published study of AFP responses during tracheal intubation and anaesthesia, Raju and colleagues [3] found a significantly greater increase in AFP in infants undergoing awake intubation compared with those paralysed before intubation. However, the infants in their report ranged in age from 7 days to 10 months and were not anaesthetized. Furthermore, two of the nine patients studied had hydrocephalus, which may have accounted for the high mean preoperative AFP (16.5 cm H_2O) and the significant increase in AFP to 27.1 cm H_2O during anaesthesia. Their report did not specify the method of fixation of the Ladd transducer. A previous investigation [6] reported variability in AFP measurement, depending on the method of application of the transducer. Subsequent work from Raju, Doshi and Vidyasager [7] has demonstrated mean ICP values of 7.1 mm Hg, 7.5 mm Hg and 8.2 mm Hg in infants of gestational ages 28–32 weeks, 33–37 weeks and 38–40 weeks, respectively. Using a method of fixation known to minimize the effects of application pressure [6], we have been able to demonstrate similar AFP values in quiet, undisturbed infants (fig. 1).

The pathogenesis of intraventricular intracranial haemorrhage suggests that increases in arterial and central venous pressures may be more important than increases in ICP [8]. In the present study, high systolic arterial pressures were observed in infants during intubation, with higher values during awake intubation than in those anaesthetized before intubation. However, these changes were not statistically significant—possibly because of the small numbers of infants studied. Kelly and Finer [4] observed increases in systolic arterial pressure of 24.7 mm Hg in infants pretreated with atropine compared with 17.8 mm Hg in those paralysed with pancuronium. In contrast, Hinkle [9] demonstrated decreases in systolic arterial pressure during 30-s periods of laryngoscopy in infants pretreated with atropine. Further studies are required to define these changes more clearly.

Awake intubation may result in periods of apnoea sufficient to cause hypercarbia or hypoxaemia, with subsequent increases in ICP [3]. However, Fisher, Frewen and Swedlow [10] were unable to demonstrate increases in ICP in children during periods of apnoea lasting 30 s. Similar periods of apnoea during laryngoscopy caused a decrease in mean transcutaneous oxygen tension (Ptc_{O_2}) to 44.2 mm Hg in neonates who had breathed 100 % oxygen for 2 min [9]. Neither arterial oxygen saturation nor Ptc_{O_2} was measured in the present study. Although there was no clinical evidence of cyanosis in any of the patients, it remains speculative as to whether short periods of hypoxaemia contributed to the increase in AFP during awake intubation.

The attenuated AFP response to intubation in the anaesthetized infant may result in part from neuromuscular blockades. Raju and colleagues [3] reported attenuated responses to intubation in infants paralysed with tubocurarine. Kelly and Finer [4] found an increase in AFP of 19.8 cm H_2O in awake neonates compared with 11.6 cm H_2O in those paralysed with pancuronium. Although suxamethonium may cause increases in ICP, White and co-workers [11] reported that the increase in ICP during tracheal suctioning in adults was attenuated to a greater extent with suxamethonium 1 mg kg^{-1} than with fentanyl, thiopentone or i.v. or intratracheal lignocaine. We postulate that paralysis attenuates the increase in AFP by preventing the increase in intrathoracic pressure which is associated with coughing and straining.

Recent concern over the increase in AFP during awake intubation may not be justified. We have demonstrated significant increases in AFP during crying in healthy infants. The paroxysmal increase in AFP during awake intubation may well be of less importance than the prolonged increases observed during crying in the healthy infant.

Awake intubation remains an important part of paediatric anaesthetic practice and further studies should be directed at identifying and attenuating the cardiovascular and ICP responses to this manoeuvre.

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COMPARISON OF ATRACURIUM-INDUCED NEUROMUSCULAR BLOCKADE IN NEONATES, INFANTS AND CHILDREN

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SUMMARY

The potency of atracurium was determined in neonates, infants and children during thiopentone–fentanyl–nitrous oxide in oxygen anaesthesia using single dose–response curves. The effective doses producing 50% depression of the first twitch of the train-of-four were significantly lower in neonates and infants than in children (82 and 112 v. *135 μg kg^{-1}). Following a standard dose of atracurium 0.5 mg kg^{-1}, 95% depression of the first twitch occurred more rapidly in neonates than in children (0.9* v. *1.4 min), while recovery to 10% of the control twitch height occurred more rapidly in neonates than in the other two groups (22.7* v. *29.7 and 28.6 min). It is concluded that neonates and infants require less atracurium to produce a given degree of neuromuscular blockade compared with older children. However, prompt recovery can be expected in all healthy paediatric patients following a standard intubating dose of atracurium 0.5 mg kg^{-1}.*

Atracurium is a non-depolarizing neuromuscular blocking drug, the duration of action of which is suitable for many paediatric surgical procedures. In view of reports suggesting that the newborn are sensitive to this type of myoneural blockade [1–5], we wished to compare the effects of atracurium in neonates, infants and children. In the present study the ED_{50} and the ED_{95} of atracurium were determined for each of the above groups during thiopentone–fentanyl–nitrous oxide in oxygen anaesthesia. In addition, we determined the speed of onset, and the duration of action, of a standard intubating dose.

PATIENTS AND METHODS

The design of the study was reviewed and approved by the District Ethics Committee. Sixty-three paediatric surgical patients consisting of 21 neonates (median age 9 days, range 1–27), 21 infants (median age 4 months, range 1.3–10.9), and 21 children (median age 4.3 yr, range 1.4–5.7) were the subjects of the study. All were ASA class I and none was receiving drugs known to interfere with neuromuscular transmission.

No premedication was given. In all patients anaesthesia was induced with thiopentone 6–8 mg kg^{-1} and fentanyl 5 μg kg^{-1}. Anaesthesia was maintained with 70% nitrous oxide in oxygen, supplemented with thiopentone, as required. With the exception of four neonates who had the trachea intubated while awake, intubation of the trachea was performed following induction of anaesthesia but without the aid of a neuromuscular blocking drug. Ventilation was controlled using the paediatric attachment of the Blease ventilator. End-tidal carbon dioxide tension was monitored using a Datex capnograph, and maintained in the range 5.0–5.5 kPa. Rectal temperature was maintained between 36.5 and 37.5 °C.

Neuromuscular transmission was monitored using the method of Ali, Utting and Gray [6]. The ulnar nerve was stimulated supramaximally at the wrist via small silver electrodes applied to the skin with adhesive electrode paste. Trains-of-four with square pulses of 0.2 ms duration at a frequency of 2 Hz were repeated every 10 s using

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a Grass S48 stimulator and SIU5 isolation unit. The hand and forearm were immobilized in a splint and the force of thumb adduction was measured using a strain gauge transducer (Grass FT03) and recorded on a pen-and-ink recorder (Grass polygraph).

Following a period of 8–12 min to allow stabilization of the train-of-four responses, atracurium was administered by rapid (5-s) i.v. injection. In order to construct dose–response curves, 15 patients from each age group were allocated randomly to three sub-groups of five. Patients in each sub-group received one of three doses of atracurium (table I), which were chosen following a preliminary trial to determine the approximate position of the dose–response curves. The remaining six patients from each group received atracurium 0.5 mg kg^{-1} to determine the onset and duration of a standard dose suitable for intubation. Onset times were measured from injection to 95 % and 100 % depression of the first twitch of the train-of-four. Recovery times were measured from injection until the initial twitch had recovered to 10 % and 25 % of the control twitch height.

Before regression analysis, doses were transformed into logarithms and depression of twitch height was transformed into probit values. These transformations convert the sigmoid dose–response relationship for neuromuscular blockade into a straight line [7, 8]. Log–probit regression lines were calculated using the iterative least squares method of Finney [9]. Calculations were performed on a PRIME 9955 computer using a Rothamstead statistical package, GLIM 3.77. The fitted lines were tested for parallelism and identity using the goodness-of-fit Chi squared and the F ratio test. The ED_{50} and ED_{95} values obtained from the regression analysis, and the onset and recovery times, are presented with their standard errors. Statistical differences were determined by analysis of variance and Student's t test for unpaired data using Bonferroni's modification for multiple comparisons. The null hypothesis was rejected when $P < 0.05$.

RESULTS

Figure 1 illustrates the fit of the regression lines with the mean dose–response data for the three groups of patients. The weighted regression coefficient (common slope) was 4.44 probits $\log^{-1}$. Allowing the slopes to differ did not improve the goodness-of-fit Chi square, so these were not significantly different. When the positions of the lines (intercepts) were compared using the F ratio test, these were found to be significantly different ($P < 0.001$), indicating that the groups differed significantly in their sensitivity to atracurium.

The values of ED_{50} and ED_{95} obtained from the regression analysis are shown in table II. It will be seen that the neonates had the lowest

TABLE I. *Subgroups and doses* (*µg* kg^{-1})

n	Neonates	Infants	Children
5	65	85	100
5	85	100	150
5	100	150	200

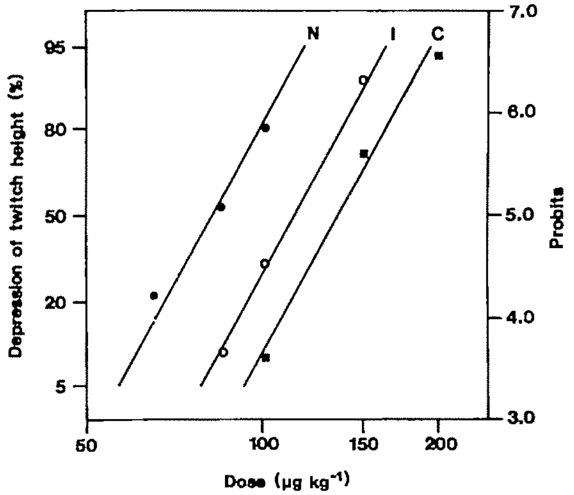

FIG. 1. Log dose–probit response regression lines for neonates (N), infants (I) and children (C). The points along the lines represent mean responses from sub-groups of five patients.

TABLE II. *Calculated values of* ED_{50} *and* ED_{95} ± *SE. The initials* N = *neonates*, I = *infants*, C = *children indicate significant differences between groups*

	Neonates	Infants	Children
ED_{50}			
(µg kg^{-1})	82±4.5	112±4.0	135±4.5
$P < 0.001$	IC	NC	NI
ED_{95}			
(µg kg^{-1})	119±8.6	163±10.1	195±10.6
$P < 0.01$	I	N	
$P < 0.001$	C		N

TABLE III. *Onset times (mean ± SEM) following atracurium 0.5 mg kg^{-1}. The initials N = neonates, C = children indicate one significant difference between groups*

	Neonates (n = 6)	Infants (n = 6)	Children (n = 6)
Time from injection to 95 % block (min)	0.9±0.1	1.0±0.1	1.4±0.1
$P < 0.05$	C		N
Time from injection to 100 % block (min)	1 1±0.2	1.2±0.2	1.7±0.1

TABLE IV. *Recovery times (mean ± SEM) following atracurium 0.5 mg kg^{-1}. The initials N = neonates, I = infants, C = children indicate significant differences between groups*

	Neonates (n = 6)	Infants (n = 6)	Children (n = 6)
Injection to 10 % control twitch height (min)	22.7±1.5	29.7±2.4	28.6±0.6
$P < 0.05$	IC	N	N
Injection to 25 % control twitch height (min)	28.7±1.9	35.9±2.5	33.7±1.2

values and almost all the differences between the groups were statistically significant.

Onset and recovery times following atracurium 0.5 mg kg^{-1} are shown in tables III and IV, respectively. The speed of onset was significantly more rapid in neonates compared with children ($P < 0.05$), whilst recovery was more rapid in neonates compared with the other two groups ($P < 0.05$).

DISCUSSION

The differences between the ED_{50} and ED_{95} values of atracurium for patients in the present study (table II) indicate that neonates and, to a lesser extent, infants are sensitive to atracurium when compared with older children. These findings agree with earlier reports of sensitivity to other non-depolarizing neuromuscular blocking agents [1–5]. Although the basis of this sensitivity is still not fully understood, it seems likely to be immaturity of neuromuscular transmission. Churchill-Davidson and Wise [10] showed that neuromuscular transmission fatigued more readily in neonates than in adults, while experimental evidence suggests that there is a reduction in the amount of acetylcholine available for release at the neuromuscular junction in the very young. From an analysis of neuromuscular transmission in rat phrenic nerve–diaphragm preparations, Kelly and Roberts [11] estimated that the rate at which acetylcholine was made available for release in 30-day-old rats was less than one-half of that in 110-day-old rats. Furthermore, they calculated that the safety factor in neuromuscular transmission in young rats—that is the number of times the amount of acetylcholine released exceeded the minimum necessary to produce a muscle action potential—was only 70–80 % of that in older rats. They suggested that a similar loss of safety factor in infants could account for the observed sensitivity to the non-depolarizing myoneural blockers.

The safety factor in neuromuscular transmission may also help to explain a discrepancy between the results of the present study and those of Goudsouzian and colleagues [12, 13]. Using a similar method for measuring neuromuscular transmission in paediatric patients, but plotting cumulative rather than single dose–response curves, these authors failed to demonstrate any difference in sensitivity to tubocurarine or metocurine between neonates, infants and children. However, because twitch height is depressed only after the safety factor has been overcome, the cumulative dose–response method underestimated the neuromuscular blocking effect of the first dose of a test drug. The error introduced to the dose–response relationship will vary with the size of the safety factor. A further practical problem in determining cumulative dose–response curves is the delay in obtaining maximum effect following subclinical doses of neuromuscular blocking drugs. In the present study the maximum effect of small doses of atracurium commonly occurred 3–4 min after administration. It is difficult to see how previous investigators could have been sure of determining the maximum effect of incremental doses of neuromuscular blockers when four or five of these were given within 8 min.

The most comparable studies with atracurium in adults give values of ED_{50} of 83 µg kg^{-1} and 100 µg kg^{-1} [14, 15]. These values are similar to our results in neonates, but less than those obtained in infants and children (table II). On this basis, it would appear that neonates require the same dose of atracurium as adults, whilst infants and children require slightly higher doses. The apparent lack of sensitivity in neonates and resistance in our older patients when compared with adults can be explained by the gradual reduction in the volume of distribution of the neuromuscular blockers (that is the extracellular fluid volume) throughout infancy and childhood. Cook [16] has shown that these differences can be resolved by expressing the doses of the myoneural blocking drugs in µg m^{-2}. Using his table of mean weights and surface areas to convert the ED_{50} values of our patients to µg m^{-2} gives the following approximate values: neonates 1212 µg m^{-2}, infants 1925 µg m^{-2}, and children 3385 µg m^{-2}. The equivalent adult value (mean of the two results presented above) is 3768 µg m^{-2}. Thus on a µg m^{-2} basis, children require about the same dose of atracurium as adults, whilst infants require half as much and neonates one-third. The results in infants and children are comparable to those obtained by Brandom and colleagues [17, 18].

Complete depression of the initial twitch of the train-of-four occurred in all patients given atracurium 0.5 mg kg^{-1} (table III). The trend towards faster onset times in neonates and infants compared with children may be explained by the rapid circulation time in these patients [19] and the shorter distribution half-life of atracurium in infants [20]. Time to 95% depression of twitch height is important because intubation can easily be carried out at this degree of neuromuscular blockade [21]. Our results indicate that atracurium 0.5 mg kg^{-1} should provide good intubating conditions in neonates and infants in about 90 s, and in children in less than 2 min. The time to 100% depression in children (1.7 min) was identical to that previously obtained in adults given atracurium 0.5 mg kg^{-1} by rapid i.v. injection [15].

Plasma clearance of atracurium is significantly greater in infants aged less than 6 months compared with children, and its elimination half-life tends to be shorter [20]. The extrapolation of these results to neonates in the present study could explain their more rapid recovery following atracurium 0.5 mg kg^{-1} (table IV). The 10% recovery time of 22.7 min in our neonatal group aged 5–27 days agrees closely with the data of Nightingale [22] on the clinical duration of effect of atracurium in neonates aged 3–28 days. Although in this earlier study clinical duration was found to be increased to 32.4 min in neonates aged less than 3 days, this is still comparable to the 10% recovery times of our infants and children and we would not regard this as an indication for reducing the initial dose of atracurium. Recovery of the first twitch to 25% of the control value was more rapid in all groups in the present study than in adults given the same dose of atracurium (43.6 min) [23].

In summary, neonates and infants require less atracurium to produce a given degree of neuromuscular block compared with older children. However, in view of the prompt rates of recovery it should be convenient to use the same initial dose of atracurium, 0.5 mg kg^{-1}, for all paediatric surgical patients.

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INCREASE IN INTRAGASTRIC PRESSURE DURING SUXAMETHONIUM-INDUCED MUSCLE FASCICULATIONS IN CHILDREN: INHIBITION BY ALFENTANIL

L. LINDGREN AND L. SAARNIVAARA

SUMMARY

Changes in intragastric pressure after the administration of suxamethonium 1.5 mg kg^{-1} i.v. were studied in 32 children (mean age 6.9 yr) pretreated with either physiological saline or alfentanil 50 µg kg^{-1}. Anaesthesia was induced with thiopentone 5 mg kg^{-1}. The incidence and intensity of muscle fasciculations caused by suxamethonium were significantly greater in the control than in the alfentanil group. The intragastric pressure during muscle fasciculations was significantly higher in the control group (16 ± 0.7 (SEM) cm H_2O) than in the alfentanil group (7.7 ± 1.5 (SEM) cm H_2O). The increase in intragastric pressure was directly related to the intensity of muscle fasciculations (regression line: $y = 0.5 + 4.78x$ with r of 0.78). It is concluded that intragastric pressure increases significantly during muscle fasciculations caused by suxamethonium in healthy children. Alfentanil 50 µg kg^{-1} effectively inhibits the incidence and intensity of suxamethonium-induced muscle fasciculations; moreover, intragastric pressure remains at its control value.

Aspiration of gastric contents to the lungs is a major hazard of general anaesthesia [1, 2]. The incidence of death in relationship to pulmonary aspiration of gastric content is higher in children than in adults [1]. Risk factors in children are the short oesophagus and the insufflation of gas to the stomach when using an anaesthetic face mask [3]. The increase in intragastric pressure in this situation may cause incompetence of the cardio-oesophageal junction and regurgitation of gastric content.

It has been demonstrated in adults that the increase in intragastric pressure is directly related to the intensity of suxamethonium-induced muscle fasciculations [4]. However, Salem, Wong and Lin [5] did not find any significant increase in intragastric pressure after suxamethonium in children. In that study, the incidence of muscle fasciculations was low, possibly because anaesthesia was induced with halothane in 67% of the children and with thiopentone in the remainder. Therefore, the intensity of muscle fasciculations may have been inhibited because halothane, like enflurane [6], decreases suxamethonium-induced depolarization at the myoneural junction [7]. Moderate or even violent muscle fasciculations have been seen in 80–100% of children given suxamethonium after thiopentone [8–10].

It has been demonstrated that fentanyl 1 or 2 µg kg^{-1} [9] and alfentanil 10, 25 or 50 µg kg^{-1} [10] inhibit muscle fasciculations caused by suxamethonium in children in a dose-dependent manner. The present study evaluated the change in intragastric pressure in children during muscle fasciculations caused by suxamethonium with or without pretreatment with alfentanil 50 µg kg^{-1}.

PATIENTS AND METHODS

The Ethics Committee of the Otolaryngological Hospital approved the study of 32 children (table I) premedicated with midazolam 0.6 mg kg^{-1} and atropine 0.03 mg kg^{-1} in red berry juice about 1 h before the induction of anaesthesia. Fifteen children received alfentanil 50 µg kg^{-1} as pretreatment: the control group received physiological saline. A nurse who was not involved in the study made up the solutions of alfentanil or saline in 5-ml syringes coded numerically; the code was not broken until the study had been completed.

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TABLE I *Characteristics of the treatment groups (mean ± SD).* n = *Number of children. Alf 50 = children pretreated with alfentanil 50 μg kg⁻¹*

	Male/Female	Age (yr)	Weight (kg)	Haemoglobin concn (g litre⁻¹)
Control ($n = 17$)	10/7	6.8±2	22.5±5	126±9
Alf 50 ($n = 15$)	9/6	7.0±2	23.5±5	126±8

TABLE II. *Intensity of visible muscle fasciculations caused by suxamethonium. Number (%) of children achieving the fasciculation score: 0 = none; 1 = mild; 2 = moderate; 3 = violent fasciculations in the abdominal musculature.* n = *Number of children.* * P < 0.001 *(Chi-square-test) compared with the control group*

	Fasciculation score			
	0	1	2	3
Control ($n = 17$)	0 (0%)	1 (6%)	8 (47%)	8 (47%)
Alf 50* ($n = 15$)	11 (73%)	4 (27%)	0 (0%)	0 (0%)

The pretreatment drug was injected as a rapid bolus 1 min before the administration of thiopentone 5 mg kg⁻¹ over 45 s. A plastic catheter (o.d. 4 mm) with an end hole and two side holes at its distal end (Pharma-plast, Denmark) was then introduced, through the right nostril, to the stomach. The length of the catheter was predetermined. The catheter was connected by a three-way stopcock to a pressure manometer (National Catheter Corp., Mallinckrodt Company). The same pressure gauge was used throughout the study. The proximal end of the catheter was fixed to the cheek. All the children were gently ventilated with 100% oxygen after insertion of the catheter. Suxamethonium 1.5 mg kg⁻¹ was injected. The intensity of visible muscle fasciculations in the abdominal musculature was scored: 0 = none; 1 = mild; 2 = moderate; 3 = violent muscle straining in the abdominal wall. The initial intragastric pressure and the changes during fasciculations were recorded by the same experienced nurse. The children were not touched during the fasciculations. The place of the distal end of the catheter was confirmed by aspirating gastric contents after intubation. Only children in whom reddish berry juice could be aspirated freely from the stomach were included in the study. Altogether 50 attempts were made. The pH of the gastric contents was estimated with a colour-indicator paper (Acilit, Merck, Darmstadt) and all the children were anaesthetized by the same author (L.L.).

Student's *t* test was used for statistical analysis of the parametric, and Chi-square test for the non-parametric, data. A regression analysis was drawn for the relationship between the changes in intragastric pressure and the intensity of muscle fasciculation.

RESULTS

Ninety percent of the control group and all of the alfentanil group were apnoeic when the initial intragastric pressure was assessed before administration of suxamethonium.

The intensity of visible muscle fasciculations in the abdominal musculature after suxamethonium was significantly greater in the control than in the alfentanil group (table II). Initial intragastric pressures were comparable in both study groups (mean 5±1 (SEM) cm H_2O). The increase in intragastric pressure was significantly greater in the control (range 6–24 cm H_2O) than in the alfentanil group (range 0–5 cm H_2O) (fig. 1). In nine of 17 children in the control group intragastric pressure exceeded 15 cm H_2O during fasciculation. The increase in intragastric pressure was directly related to the intensity of muscle fasciculations (fig. 2). The mean pH of gastric content in 32 children was 1.9±0.07 (SEM).

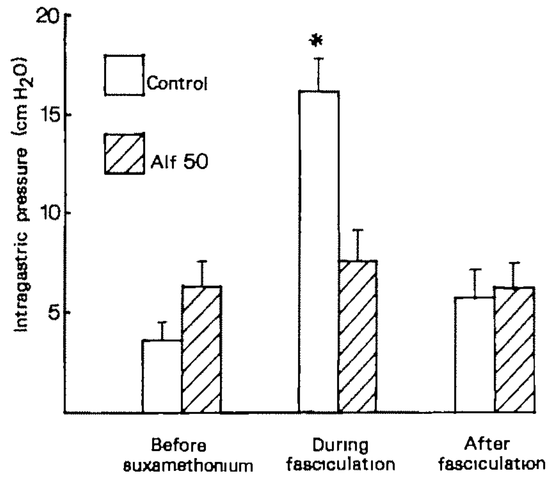

FIG. 1. Changes in intragastric pressure in 32 children during muscle fasciculations caused by suxamethonium. Alf 50 = the group pretreated with alfentanil 50 µg kg^{-1}. $*P < 0.001$ from the control group (Student's t test).

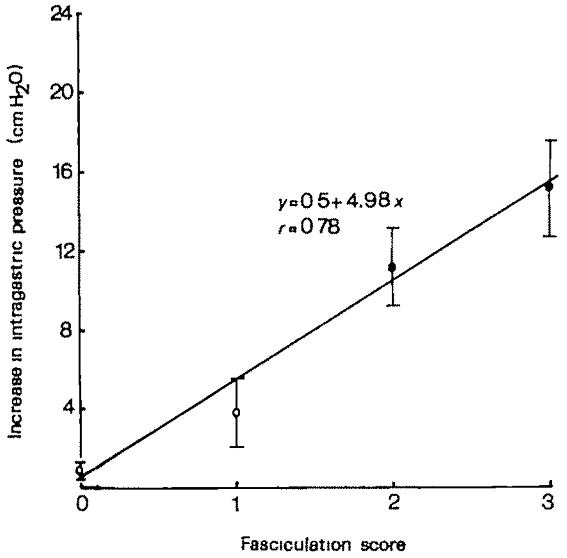

FIG. 2. Relationship between the intensity of muscle fasciculations in the abdominal musculature. Fasciculation score: 0 = none; 1 = mild; 2 = moderate; 3 = violent. Bars indicate SEM. Open circles = mean values in the alfentanil 50 µg kg^{-1} pretreated group; closed circles = mean values in the control group. Regression line for 32 points: $y = 0.5 + 4.98x$; $r = 0.78$ ($P < 0.001$).

DISCUSSION

These results show that the intragastric pressure increased significantly during muscle fasciculations caused by suxamethonium in children. Alfentanil 50 µg kg^{-1} effectively inhibited fasciculations as well as the increase in intragastric pressure.

In the present study, the incidence of suxamethonium-induced fasciculations was 100% after induction with thiopentone. In 47% of the children who did not receive alfentanil, the fasciculations were violent. The increase in intragastric pressure correlated directly with the intensity of muscle fasciculations. The relationship between the increase in intragastric pressure and the intensity of muscle fasciculations noted here was almost identical to that obtained by Miller and Way [4] in young muscular men. The initial intragastric pressures and the increases during fasciculation were equal to those demonstrated by Smith, Dalling and Williams [11] in adults.

A balloon-tip catheter has been used in previous studies for measuring intragastric pressure [4, 5, 12, 13] to prevent the gastric mucosa occluding the opening of the catheter during a sudden increase in intragastric pressure. In this study, a catheter without a balloon tip, but with three openings, was used to ensure patency. Air may bypass a catheter without a balloon tip and escape from the stomach during fasciculations. If this is so, increases in intragastric pressure may be underestimated, but a balloon-tip catheter may induce gastric contractions to give erronous data as postulated by Smith, Dalling and Williams [11].

According to data from previous studies, an intragastric pressure of less than 15 cm H_2O can open the cardio-oesophageal junction [14, 15]. If this is so 47% of the children in the present study would have been at risk of regurgitation. Since violent muscle fasciculations have been reported in younger children [6, 8, 9] than those studied here, it is likely that intragastric pressure would increase in them also. If regurgitation occurs that easily in children, the incidence of aspiration pneumonitis would definitively be greater. The lower oesophageal sphincter (LOS) is the major barrier to regurgitation of gastric contents into the oesophagus [16, 17]. LOS function is normal by the age of 6 weeks [18], but gastro-oesophageal reflux is common in children with mental retardation [19] or with tracheo-oesophageal fistula [20]. Atropine decreases LOS tone [17, 21], but no increased risk of regurgitation was noted in adults who had not received anticholinergic premedication, since LOS pressure increased simultaneously with the intragastric pressure [11]. It is evident that regurgitation would have been inhibited by the LOS pressure in the healthy children in the present study although LOS pressure was not measured. However, the effect of atropine premedication on LOS competence in the presence of increased intragastric pressure during muscle fasciculations in children remains to be evaluated.

The mechanism of the inhibitory action of alfentanil on suxamethonium-induced muscle fasciculations remains unexplained. Morphine and nalorphine inhibit neuromuscular transmission in mammalian and amphibian neuromuscular preparations by impairing the release of acetylcholine [22, 23]. Also, resting tension of the indirectly-stimulated rat hemidiaphragm increases slowly in the presence of high concentrations of morphine [22]. Thus, opioids may have neuromuscular effects.

The present results show that, in healthy children, the intragastric pressure increased significantly during suxamethonium-induced muscle fasciculations but remained unchanged in the absence of fasciculations. An increase in intragastric pressure during fasciculations has not been demonstrated previously in children. This increase may not be clinically important, since a protective increase in LOS pressure has been shown to occur simultaneously in adults. In those situations in which the increase in intragastric pressure in children is undesirable, the use of non-depolarizing neuromuscular blocking drugs such as tubocurarine and alcuronium, or of fentanyl [9] or alfentanil [10] provides effective protection against the muscle fasciculations caused by suxamethonium.

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EFFECT OF ADRENALINE ON EXTRADURAL ANAESTHESIA AND PLASMA BUPIVACAINE CONCENTRATIONS DURING CAESAREAN SECTION

R. S. LAISHLEY, B. M. MORGAN AND F. REYNOLDS

SUMMARY

The effect of adrenaline on the efficacy of extradural block and plasma bupivacaine concentrations was investigated in women undergoing elective ($n = 40$) and emergency ($n = 40$) Caesarean section. Patients were randomly allocated within these two groups to receive 0.5% bupivacaine 20 ml either plain or with adrenaline 1 in 200000, as a single fractionated extradural injection. The elective plain group needed significantly more supplementary analgesia compared with the other three groups ($P < 0.05$). In the elective group, plasma bupivacaine concentrations were significantly lower in the subgroup receiving extradural adrenaline than in the plain subgroup. This effect was not observed when comparing only those who received bupivacaine 100 mg. In the emergency group, there were no significant differences in plasma bupivacaine concentrations between the plain and adrenaline subgroups. Maximum plasma concentrations correlated significantly ($P < 0.0001$) with dose of bupivacaine ($mg\ kg^{-1}$). It is concluded that extradural adrenaline does not usefully reduce systemic absorption of 0.5% bupivacaine, but may improve its efficacy in extradural anaesthesia for elective Caesarean section.

There have been few thorough investigations on the effect of adrenaline on the systemic absorption of bupivacaine from the extradural space in pregnant women, and controversy remains. Reynolds and Taylor [1] reported that extradural adrenaline slightly decreased the plasma concentrations of bupivacaine during labour with no prolongation of analgesia. Reynolds, Hargrove and Wyman [2] demonstrated a significant decrease in plasma concentrations at delivery after 0.5% bupivacaine with adrenaline for extradural analgesia during labour. Abboud and colleagues [3] reported prolongation of analgesia, but no significant effect on plasma bupivacaine concentrations following extradural adrenaline. Symptoms of bupivacaine toxicity are observed rarely during labour, but the large doses used for Caesarean section may result in plasma concentrations which approach or exceed the threshold for systemic toxicity [4, 5]. In emergency Caesarean section, moreover, a large dose of bupivacaine after prolonged administration during labour may result in systemic toxicity [6].

If the systemic absorption of bupivacaine is significantly decreased by adrenaline, women receiving a large dose of bupivacaine for Caesarean section may benefit most from this effect. We have investigated the effect of adrenaline 1 in 200000 on extradural blockade and the systemic absorption of bupivacaine in women undergoing emergency and elective Caesarean section.

PATIENTS AND METHODS

Healthy women undergoing elective ($n = 40$) and emergency ($n = 40$) Caesarean section, under extradural blockade, were studied following ethical committee approval and once informed consent

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had been obtained. All patients received 0.3-mol litre^{-1} sodium citrate 30 ml and an i.v. infusion of Hartmann's solution. The ECG was monitored continuously. Within each group, mothers were randomly allocated to receive 0.5% bupivacaine 20 ml either plain or with adrenaline 1 in 200000, as commercially available.

Extradural technique

For elective Caesarean section, the mid-lumbar extradural space was located with a 16-gauge Tuohy needle. The local anaesthetic was injected through the needle and the extradural catheter inserted subsequently. This method is reported in detail elsewhere [7]. For emergency Caesarean section, all mothers had already received plain bupivacaine via an extradural catheter during labour, and the dose for Caesarean section was injected through the catheter. In all cases a 2-ml test dose was followed after 5 min by the remaining 18 ml of local anaesthetic injected over 5 min. All patients were in the left lateral position during the injection and then turned to the other side for a further 5 min. After this, they were placed supine with a wedge under the right buttock.

The onset and progress of the extradural block was assessed over 30 min at 5-min intervals as described in detail elsewhere [7]. If the height of the block was below T6 at 20 min, a supplementary dose (up to 10 ml) of 0.5% plain bupivacaine was administered. Nitrous oxide, i.v. opioids or supplementary 0.5% plain bupivacaine were administered if pain or discomfort occurred during surgery.

All patients were observed closely for the development of hypotension (systolic arterial pressure < 100 mm Hg), nausea and symptoms of bupivacaine toxicity (drowsiness, circumoral paraesthesia, hearing changes). Hypotension was treated by increasing the rate of the infusion of Hartmann's solution, and by the administration of ephedrine 15 mg i.m. and 15 mg i.v. Nausea was treated by correction of any associated hypotension and i.v. metoclopramide. All women received oxygen via MC mask until delivery, when Syntocinon 10 units i.v. was administered slowly.

Bupivacaine plasma concentrations

Maternal venous blood samples (5-ml heparinized) were withdrawn through an i.v. cannula and three-way tap inserted to a vein in the arm contralateral to that receiving the i.v. infusion. Samples were taken just before the 20-ml bupivacaine dose in the emergency Caesarean section group (0 min) and after 10, 20, 30 and 45 min in all patients. After separation by centrifugation, plasma samples were stored at 4 °C until assayed. Bupivacaine was measured by gas chromatography using the method of Reynolds and Beckett [8], but with 1-ethyl-2′,6′-pipecholylxylidine, the ethyl homologue of bupivacaine, as the internal marker, 3% OV17 as stationary phase, and a nitrogen detector.

Statistics

Statistical evaluation of the data was carried out using the SAS Statistical Package running on the Amdahl V8 computer at the University of London Computer Centre. The GLM procedure was used to perform a repeated measures Analysis of Variance on plasma concentrations. One-way analysis of variance with Tukey's multiple comparison test, Student's *t* test, Kruskall–Wallis test, Fisher's exact test or the Chi-square test were used for all other calculations.

RESULTS

The clinical data are shown in table I. There were no significant differences in age, weight or height between the groups.

The doses of bupivacaine required for Caesarean section are shown in table II. Significantly more women in the elective plain group than in the emergency groups required more than the initial 100-mg dose for Caesarean section. The emergency patients were given a wide range of doses of bupivacaine during labour (table III) and there was no significant difference between plain and adrenaline groups in total dose, duration of analgesia during labour, number of additional doses or the time interval from last "top-up" to the dose before the Caesarean section.

Efficacy of extradural block for surgery

Details of the efficacy of the block in the elective group are presented elsewhere [7]. In table IV the requirement for analgesic supplementation after the initial 100-mg dose of bupivacaine for Caesarean section is summarized. The elective plain group needed significantly more supplementary analgesia compared with the other three groups ($P < 0.05$). One patient in the emergency group received general anaesthesia as she developed sudden unmanageable fear despite an apparently

TABLE I. *Clinical data (mean (SD))*

	Elective		Emergency	
	Plain ($n = 20$)	Adrenaline ($n = 20$)	Plain ($n = 20$)	Adrenaline ($n = 20$)
Age (yr)	31.0 (6.7)	28.9 (5.8)	30.2 (4.4)	30.7 (4.7)
Weight (kg)	76.3 (15.8)	72.0 (8.6)	74.6 (14.1)	76.0 (11.8)
Height (m)	1.64 (0.05)	1.64 (0.11)	1.63 (0.09)	1.61 (0.07)

TABLE II. *Caesarean section doses of bupivacaine (CSD) (no. women) and mean (SD) time from CSD to delivery*

	Elective		Emergency	
CSD	Plain ($n = 20$)	Adrenaline ($n = 20$)	Plain ($n = 20$)	Adrenaline ($n = 20$)
100 mg	13	17	19	19
135 mg	2	0	0	0
140 mg	2	0	0	0
150 mg	2	3	1	1
275 mg	1	0	0	0
CSD to delivery interval (min)	54.4 (20.4)	46.9 (7.2)	38.6 (12.8)	34.7 (10.3)

TABLE III. *Emergency Caesarean sections: details of extradural analgesia before Caesarean section dose (CSD) (mean values ± SD (range))*

	Plain ($n = 20$)	Adrenaline ($n = 20$)
Duration of extradural analgesia before CSD (min)	408 ± 214 (55–915)	395 ± 233 (10–780)
Number of extradural top ups before CSD (range)	1–9	1–10
Total dose bupivacaine plain before CSD (mg)	121 ± 80 (43–328)	113 ± 70 (25–324)
Time from last extradural top up to CSD (min)	114 ± 57 (40–230)	98 ± 55 (35–215)

TABLE IV. *Efficacy of extradural block: number of patients requiring supplementary analgesia following the initial 100-mg dose of bupivacaine.* **P < 0.05 compared with other three groups*

	Elective		Emergency	
	Plain ($n = 20$)	Adrenaline ($n = 20$)	Plain ($n = 20$)	Adrenaline ($n = 20$)
Nil	11*	15	18	18
Supplementary bupivacaine only	3	3	0	1
Nitrous oxide/opiates only	2	2	0	1
Bupivacaine plus N_2O/opiates	4*	0	1	0
General anaesthesia	0	0	1	0

satisfactory extradural block. Extradural anaesthesia was sufficient alone in 32 elective patients (80%) and 37 emergency patients (93%). The modal height of block had reached T3 at 30 min in 48% of elective patients and 45% of emergency patients. Adrenaline had no effect on spread of extradural block.

Plasma bupivacaine concentrations

Mean plasma bupivacaine concentrations in the four groups are shown in figure 1. In the elective group, extradural adrenaline was associated with a significant reduction in bupivacaine concentrations, but in those who received only bupivacaine 100 mg (table II) there were no significant differences between the plain and adrenaline groups. In the emergency group adrenaline had no significant effect on bupivacaine concentration. Bupivacaine concentrations were significantly greater ($P < 0.0001$) in the combined emergency groups than in the combined elective groups (fig. 2), but not significantly different in the combined adrenaline groups compared with the combined plain groups (fig. 3).

The use of extradural adrenaline was not associated with a significant reduction in maximum bupivacaine concentration (C^{max}) (table V). Time to C^{max} was significantly longer in the elective plain group than in the other three groups ($P < 0.01$), reflecting the fact that more supplementary doses of bupivacaine were necessary in the elective plain group. C^{max} increased significantly with dosage of bupivacaine (mg kg^{-1}) in the whole population ($r = 0.618$; $P < 0.0001$) and in the elective ($P < 0.001$), emergency ($P < 0.026$), plain ($P < 0.0002$) and adrenaline ($P < 0.0001$) groups (fig. 4). C^{max} was negatively correlated ($r = -0.425$; $P < 0.001$) with bupivacaine dose rate (total dose/first dose to delivery interval). In only three patients did C^{max} exceed the oft quoted minimum toxic threshold of 1.6 $\mu g\ ml^{-1}$ [9–11]. All had received plain bupivacaine. One elective

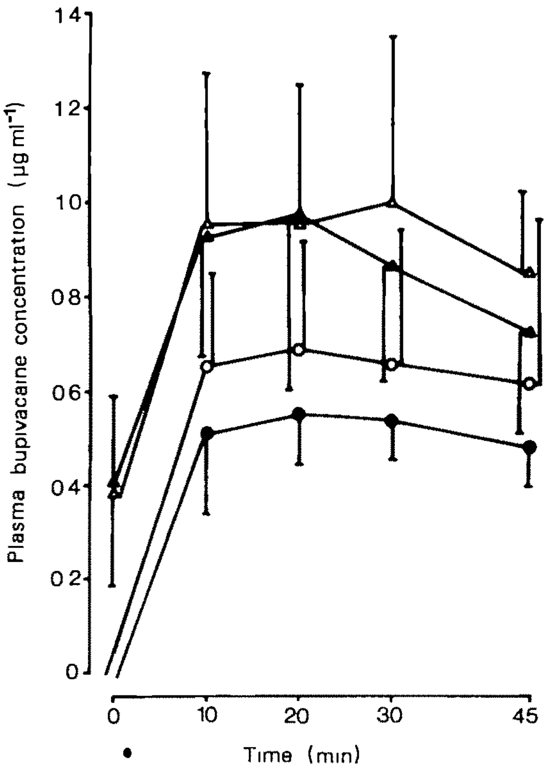

FIG. 1. Plasma bupivacaine concentration (mean ± SD) for all patients: emergency plain (△——△), emergency adrenaline (▲——▲), elective plain (○——○), elective adrenaline (●——●). Significant difference ($P < 0.05$) between elective plain and elective adrenaline at all sampling times.

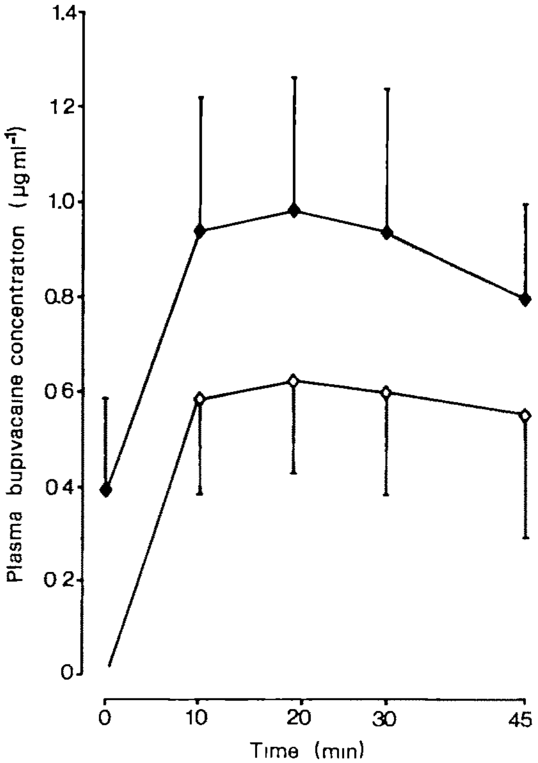

FIG. 2. Plasma bupivacaine concentrations (mean ± SD) for all patients: emergency (◆——◆) compared with elective (◇——◇). Significant difference ($P < 0.05$) between the groups at all sampling times.

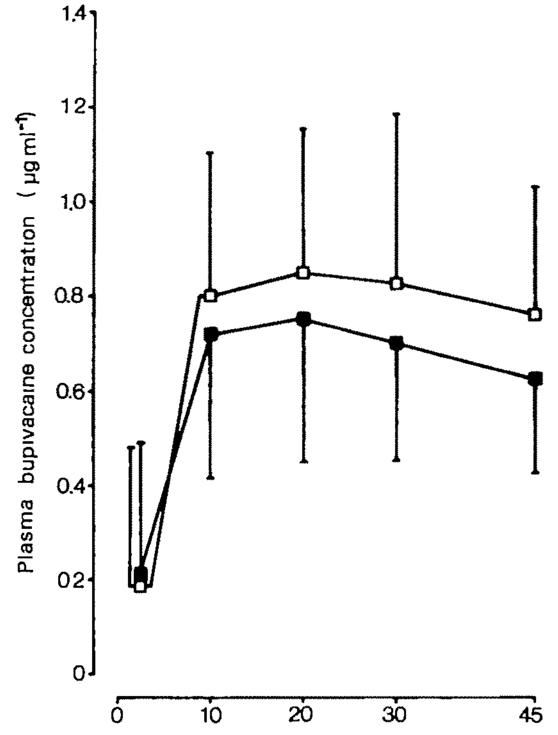

FIG. 3. Plasma bupivacaine concentrations (mean ± SD) for all patients: plain (□——□) compared with adrenaline (■——■). No significant difference between the groups.

patient (1.97 µg ml^{-1}) had received the unusually high dose of bupivacaine 275 mg (3.7 µg ml^{-1}) over a 2-h period while two emergency patients (1.73 and 1.86 µg ml^{-1}) had both received bupivacaine 100 mg for Caesarean section following only 87 mg and 103 mg, respectively, during labour.

Complications

Drowsiness was observed in 16 patients who had maximum plasma bupivacaine concentrations ranging from 0.53 to 1.53 µg ml^{-1}. However, none of the three patients with maximum bupivacaine concentrations greater than 1.6 µg ml^{-1} had symptoms of toxicity. No other toxic symptoms occurred.

The incidence of hypotension, nausea, vomiting and shivering among the four groups is given in table VI. In the elective group, shivering occurred more frequently after adrenaline than after plain solution ($P < 0.05$). There were no other significant differences among the groups.

DISCUSSION

Our study with 0.5 % bupivacaine confirms the general belief that adrenaline may improve the efficacy of extradural local anaesthesia [12], but this effect was seen only in association with

TABLE V. *Maximum bupivacaine concentration (C^{max}) (mean (SD)). †CSD 100 mg: data presented for mothers receiving a bupivacaine dose of only 100 mg for Caesarean section. *P < 0.05 compared with other three groups*

	Elective		Emergency	
	Plain	Adrenaline	Plain	Adrenaline
Time to C^{max} (min)	29.1 (13.4)*	22.8 (12.8)	15.6 (11.9)	16.3 (13.5)
C^{max} (all patients) (µg ml^{-1})	0.80 (0.35)	0.62 (0.12)	1.11 (0.34)	1.02 (0.26)
C^{max} (CSD, 100 mg)† (µg ml^{-1})	0.73 (0.25) (n = 13)	0.61 (0.11) (n = 17)	1.10 (0.34) (n = 19)	1.04 (0.26) (n = 19)

TABLE VI. *Number of patients experiencing complications. *P < 0.05 compared with the elective adrenaline group*

	Elective		Emergency	
	Plain (n = 20)	Adrenaline (n = 20)	Plain (n = 20)	Adrenaline (n = 20)
Hypotension (systolic AP < 100 mm Hg)	6	5	8	8
Nausea/vomiting	11	7	7	7
Shivering	6*	13	10	11

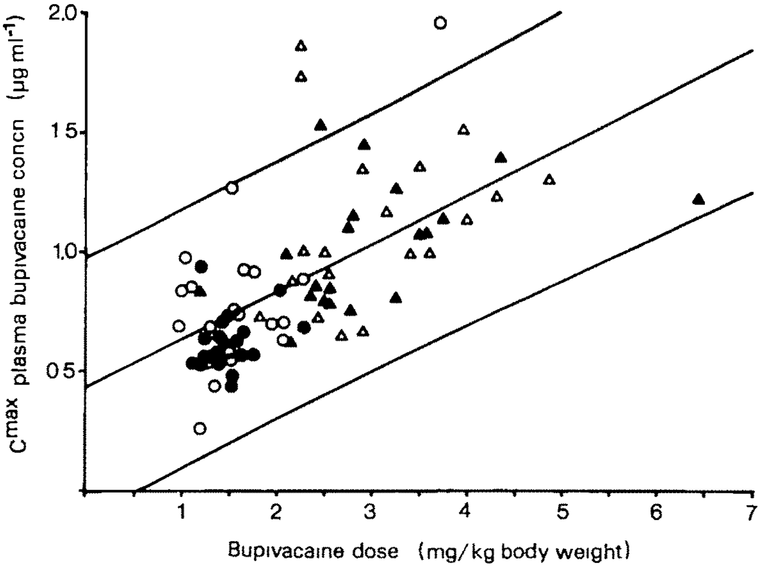

FIG. 4. Maximum plasma bupivacaine concentrations (C^{max}) plotted against bupivacaine dose per body weight for all patients: emergency plain (△——△), emergency adrenaline (▲——▲), elective plain (○——○), elective adrenaline (●——●). Correlation coefficient 0.61; $P < 0.0001$; regression line with 95 % confidence intervals.

elective Caesarean section, as the standard 100-mg dose was less likely to require enhancement by adrenaline in the presence of pre-existing extradural blockade. Adrenaline may be necessary to fortify rather low doses. Thus Littlewood and co-workers [13] found that adrenaline only improved analgesia with the more dilute solutions of bupivacaine (0.25 % and 0.125 %), and Eisenach, Grice and Dewan [14] reported that adrenaline, added to 10 ml of 0.25 % bupivacaine, improved analgesia in labour.

Adrenaline has been reported to reduce mean peak plasma concentrations of both lignocaine and bupivacaine in non-pregnant patients [15]. In our study, adrenaline was associated with significantly reduced bupivacaine concentrations only in patients undergoing elective Caesarean section; however, this effect was not observed when comparing those patients who received only the initial dose of bupivacaine 100 mg. This suggests that, in this study, any reduction in plasma bupivacaine concentration was associated with a reduced dose requirement rather than with slower systemic absorption of the drug, a finding which is of clinical relevance. Adrenaline did not usefully reduce plasma bupivacaine concentration in the emergency Caesarean section group, in which the two subgroups received similar doses of bupivacaine for Caesarean section. All these women had, moreover, received plain bupivacaine for routine extradural analgesia during labour.

Relatively high plasma bupivacaine concentrations during Caesarean section were reported by Thompson and colleagues [4]. However, their calculations measured bupivacaine as the hydrochloride salt. True bupivacaine concentrations would, therefore, be 88 % of those reported. In addition, as the internal marker they used lignocaine, which is notoriously unreliable compared with the ethyl-pipecholylxylidine used here (F. Reynolds, personal observation; R. Boyes, personal communication). Our results do not support their view that a single-dose extradural injection for elective Caesarean section leads to plasma bupivacaine concentrations similar to those observed in emergency Caesarean section. The different rates of injection, 20 ml over 20 s in their study compared with 10 min in the present study, may also account for these differences. As there is no clinical advantage from rapid injection [16] we advocate slow injection, which will also reduce the danger from accidental i.v. injection [17].

The relationship of C^{max} to drug dosage may predict the risk of reaching the threshold of toxicity. The results of our study show that there is a good correlation ($P < 0.0001$) between C^{max} and bupivacaine dose (fig. 4), but not dose rate (mg h^{-1}). This confirms the findings of Reynolds, Hargrove and Wyman [2] that maternal bupivacaine concentration is dependent on total dose rather than dose rate and reflects the fact that, during continuous administration at a constant rate, plasma concentrations of a drug reach a plateau between four to seven half-lives. Alterations in dose rate preferentially affect the ultimate plateau concentration, which is unlikely to be attained during the course of labour.

The only symptom of bupivacaine toxicity was drowsiness, which was not always observed in those patients with high bupivacaine concentrations. This emphasizes the variability among patients in their susceptibility to local anaesthetic toxicity. Shivering, which occurred in 50% of patients, has been attributed to stimulation of thermosensitive tissue in the extradural space [18].

From our study, we conclude that adrenaline may improve the effectiveness of extradural anaesthesia in elective Caesarean section, but only usefully reduces plasma bupivacaine concentration in pregnant women by virtue of reducing the dose requirement. In addition, we conclude that, using our technique, plasma concentrations of bupivacaine do not often reach the toxic threshold and, although systemic reactions may result from inadvertent i.v. injection or excessive dosage, they are unlikely to follow the correct extradural placement of an appropriate dose of bupivacaine.

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SPINAL ANAESTHESIA WITH HYPERBARIC BUPIVACAINE

Effects of Age on Neural Blockade and Pharmacokinetics

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SUMMARY

Effects of ageing were studied on the neural blockade and the pharmacokinetics after subarachnoid administration of 0.5% bupivacaine 3 ml in 8% glucose in two groups of 15 male patients, between 20 and 55 yr and older than 55 yr, respectively. The blockade was performed with the patient in the sitting position. Two minutes after the injection the patient was placed in the supine position. The time to maximum cephalad spread and the upper level of analgesia increased with advancing age, whereas the time to onset of motor blockade decreased with advancing age. Effects of age on the total duration of analgesia and motor blockade could not be demonstrated. Age had no effect on the peak plasma concentration of bupivacaine. The time to peak concentration and the terminal half-life increased, whereas the total plasma clearance decreased with advancing age.

With advancing age the central and peripheral nervous systems degenerate [1, 2]. These changes may have an impact on both the dose requirement of local anaesthetics and the quality and duration of the neural blockade. With extradural administration of bupivacaine, ageing results in a more extensive spread of analgesia and a more rapid onset of analgesia at the caudad segments [3, 4]. With subarachnoid administration of glucose-free bupivacaine, ageing results in a more rapid onset of analgesia and a decrease of the time to attain the maximum degree of motor blockade [5, 6], in addition to a slight increase of the spread of analgesia [5, 7] and a longer duration of analgesia [6].

Data on the impact of ageing on the clinical effects following subarachnoid injection of hyperbaric solutions are scarce. With hyperbaric amethocaine no effects of ageing have been observed [8, 9]. Reports on the effects of ageing after subarachnoid injection of hyperbaric bupivacaine solutions are lacking and they cannot be inferred from data derived from studies with glucose-free bupivacaine, because the addition of glucose alters the local anaesthetic profile of bupivacaine: with hyperbaric solutions the quality and duration of motor blockade of the lower limbs decrease and the duration of analgesia is shortened [10–13].

Ageing also affects the pharmacokinetics of local anaesthetics. In two recent studies [4, 6] we demonstrated an increase of the terminal half-life after extradural administration of bupivacaine and an increase of the peak plasma concentration after subarachnoid administration of glucose-free bupivacaine. In both studies ageing resulted in a marked reduction of the total plasma clearance of bupivacaine. Effects of ageing on the pharmacokinetics after subarachnoid administration of hyperbaric bupivacaine solutions have not been reported. Again, these effects cannot be inferred from data obtained with glucose-free bupivacaine solutions, because the pharmacokinetic profiles after administration of hyperbaric and glucose-free solutions differ: in younger patients a difference in the time to peak plasma concentrations of bupivacaine has been established [14, 15].

In this study we have investigated the influence of ageing on both the quality and duration of the neural blockade, and on the plasma concentration profiles after subarachnoid administration of a hyperbaric solution of bupivacaine.

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TABLE I. *Patient characteristics (mean ± SD). In group 1 patients were aged between 20 and 55 yr, in group 2 patients were older than 55 yr*

	n	Age (yr)	Weight (kg)	Height (cm)
Group 1	15	33 ± 10	78 ± 10	179 ± 8
Group 2	15	73 ± 9	80 ± 7	177 ± 7

PATIENTS AND METHODS

Thirty male patients (20–86 yr, ASA status I–II) undergoing minor orthopaedic, urological or lower abdominal surgery were enrolled in the study. After approval by the Committee on Medical Ethics of the University Hospital, informed consent was obtained from each patient. Patients were allocated to two groups according to their age (table I). Patients with a history of neurological disease, hepatic disease or bleeding diathesis were excluded from the study.

Premedication consisted of lorazepam 1–2 mg sublingually, 1.5 h and atropine 0.25–0.5 mg i.m., 45 min before the spinal procedure. A rapid i.v. infusion of dextrose in saline 500 ml was administered before the subarachnoid injection. Thereafter the infusion rate was maintained at 2 ml kg^{-1} h^{-1}. A central venous catheter was placed in the superior vena cava via the basilic or the cephalic vein after local infiltration with 0.5% lignocaine, the catheter being advanced until the tip was located at least 6 cm proximal to the junction of the azygos vein and the superior vena cava. The correct location of the catheter tip was verified by radiography.

After local infiltration of the skin with 0.5% lignocaine the dural puncture was performed with a 25-gauge spinal needle through an 18-gauge introducer, using a midline approach at the L3/4 space. During the procedure the patient was sitting. When a free flow of clear cerebrospinal fluid was obtained and after aspiration, the local anaesthetic was injected without barbotage at a rate of approximately 0.15 ml s^{-1}. After injection of 0.5% bupivacaine 3 ml in 8% glucose the patient remained sitting for 2 min and was then placed in the supine horizontal position. During the operation no sedatives were administered. Systemic arterial pressure, measured with an automatic cycling device (Accutorr 1, Datascope) and heart rate (from the ECG) were monitored during induction and surgery, and in the recovery room. If the systolic arterial pressure decreased more than 30% below the preanaesthetic value or to less than 100 mm Hg, ephedrine 5 mg was given i.v.

Analgesia was assessed and defined as absence of pain to pinprick. Motor blockade was evaluated bilaterally using a modified Bromage classification by asking the patient to raise the extended leg, flex the knee and flex the ankle, and was rated per joint (0 = no, 1 = partial, 2 = complete blockade). The results obtained for both extremities were added, giving a maximum score of 12 (complete motor blockade). Assessments were made every 5 min during the first 30 min after the injection, then at 15-min intervals until complete recovery. The following variables were calculated:

time to initial onset of analgesia at the L1/2 dermatomes;
time to initial onset of motor blockade;
time until maximum cephalad spread of analgesia;
time until maximum caudad spread of analgesia;
highest level of analgesia;
maximum number of segments blocked;
maximum score of motor block;
time until the level of analgesia had receded two segments;
time until recovery of analgesia at the T12 dermatome;
time until total disappearance of analgesia;
time until total recovery from motor blockade.

Central venous blood samples (5 ml) were collected before the spinal injection and 5, 10, 15, 20, 25, 30, 35, 40, 50, 60, 90, 120, 150, 240, 360, 480, 600, 720, 960, 1200 and 1440 min after injection. Plasma was separated by centrifugation at 2.500 *g*, stored at −20 °C and assayed for bupivacaine using a capillary gas chromatographic method with a coefficient of variation less than 6% [16]. The individual peak plasma concentrations (C^{max}) of bupivacaine, and the time at which these were reached (T^{max}) were determined. Terminal half-lives ($T_{\frac{1}{2}}^{z}$) were calculated from the rate constants (k_z) obtained by linear regression analysis of the log-linear part of the plasma concentration *v.* time curve:

$$T_{\frac{1}{2}}^{z} = 0.69/k_z$$

The area under the plasma concentration–time curve (AUC) was determined using the linear trapezoidal rule, including extrapolation to infinity [17]. The mean plasma clearance (*Cl*) was calculated according to the following equation:

$$Cl = D/\mathrm{AUC}$$

where D is the administered dose.

Values were expressed as mean ± SD. Statistical comparisons were undertaken with the Mann–Whitney U test. Spearman rank correlation coefficients were calculated to show the interrelationships between the upper level of analgesia and age, and between $T^{\max}$ and age. The relationship between the clearance and age was determined by linear regression and correlation analysis. $P < 0.05$ was considered statistically significant.

RESULTS

In all patients analgesia attained a level high enough to provide analgesia for surgery; no supplementary analgesic or sedative medication was necessary. No serious cardiovascular changes occurred. One elderly patient (81 yr) required ephedrine 5 mg i.v. for treatment of hypotension below 100 mm Hg. The mean decrease from control mean arterial pressure during the first 1 h did not exceed 10 % in the young and 15 % in the old patient group. There was no statistical correlation between the height of the block and the decrease in mean arterial pressure in either group. Postspinal headache developed in one younger patient (24 yr), and was treated successfully with a single extradural blood patch.

All blocks were symmetrical; no patient developed a level of analgesia that varied by more than one segment between the two sides of the body. The spread of analgesia during the first 30 min after the administration is presented in figure 1. After 10, 15, 20 and 30 min the older patients developed a significantly higher spread

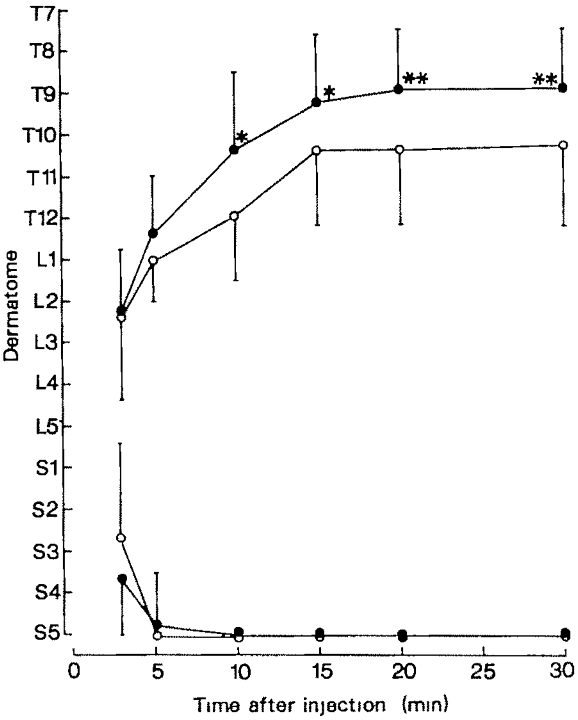

FIG. 1. Mean cephalad and mean caudad spread of analgesia at times up to 30 min in the older (●——●) and younger (○——○) patient groups. (SD bars in only one direction.) Differences between the older and younger patient groups: $*P < 0.05$; $**P < 0.01$.

TABLE II. *Characteristics of neural blockade after subarachnoid administration of 0.5% hyperbaric bupivacaine (mean ± SD)*

	Group 1	Group 2	P
Analgesia			
Initial onset time (min)	3.7 ± 0.8	3.9 ± 1.0	
Time to maximum cephalad spread (min)	10.9 ± 4.0	14.1 ± 3.2	< 0.05
Time to maximum caudad spread (min)	4.6 ± 2.3	3.7 ± 0.9	
Maximum number of segments blocked	11.9 ± 1.5	13.6 ± 2.0	
Highest level (T dermatome)	11.1 ± 1.6	8.7 ± 1.8	< 0.01
Duration highest level (min)	58 ± 26	70 ± 25	
Two-segment regression (min)	88 ± 31	104 ± 28	
Time to recovery at T12 (min)	95 ± 28	139 ± 39	< 0.01
Time to total recovery (min)	357 ± 53	335 ± 67	
Motor blockade			
Initial onset time (min)	6.2 ± 2.9	3.9 ± 1.2	< 0.01
Time to maximum degree (min)	12.3 ± 5.2	10.3 ± 4.6	
Patients with complete block (%)	67	87	
Time to total recovery (min)	167 ± 49	192 ± 36	

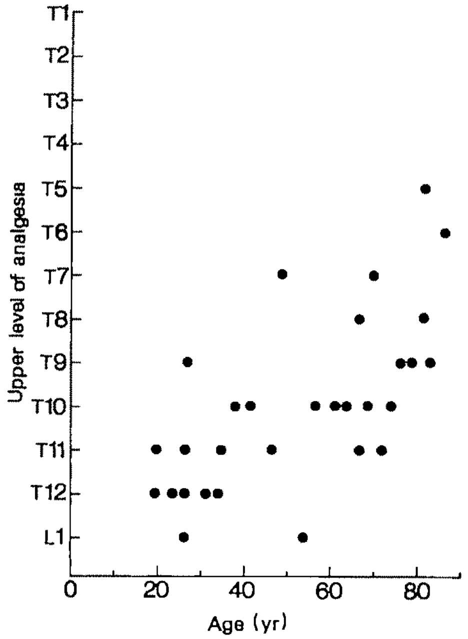

FIG. 2. Relationship between the upper level of analgesia and age after subarachnoid administration of hyperbaric 0.5% bupivacaine 3 ml.

TABLE III. *Pharmacokinetic data obtained after subarachnoid administration of 0.5% hyperbaric bupivacaine (mean ± SD)*

	T^{max} (min)	C^{max} (ng ml^{-1})	$T_{\frac{1}{2}}^{z}$ (min)	Cl (ml min^{-1})
Group 1	65 ± 38	71 ± 28	334 ± 64	525 ± 172
Group 2	107 ± 28	75 ± 23	427 ± 138	366 ± 134
P	< 0.01		< 0.05	< 0.01

compared with the younger patients. The time to maximal cephalad spread was significantly longer and the upper levels of analgesia were significantly higher in older patients (table II). In addition there was a moderate correlation between the maximal height of analgesia and age ($r_s = 0.74$, $P < 0.005$) (fig. 2). No differences were found in caudad spread between the two groups. The time to initial onset of motor blockade was significantly shorter in the group of older patients ($P < 0.01$), but the time at which the maximum degree of motor blockade was attained was similar in both groups. Complete motor blockade of the lower limbs occurred in 10 of the 15 younger patients and in 13 of the 15 older patients.

Age had no effect on the disappearance of analgesia from the two upper dermatomes. The time to recovery from analgesia at the level of T12 was longer in the older patient group ($P < 0.01$). Age did not influence the total durations of analgesia and motor blockade.

Figure 3 shows representative examples of plasma concentration *v.* time curves of an older and a younger patient. The results of the pharmacokinetic analysis are shown in table III.

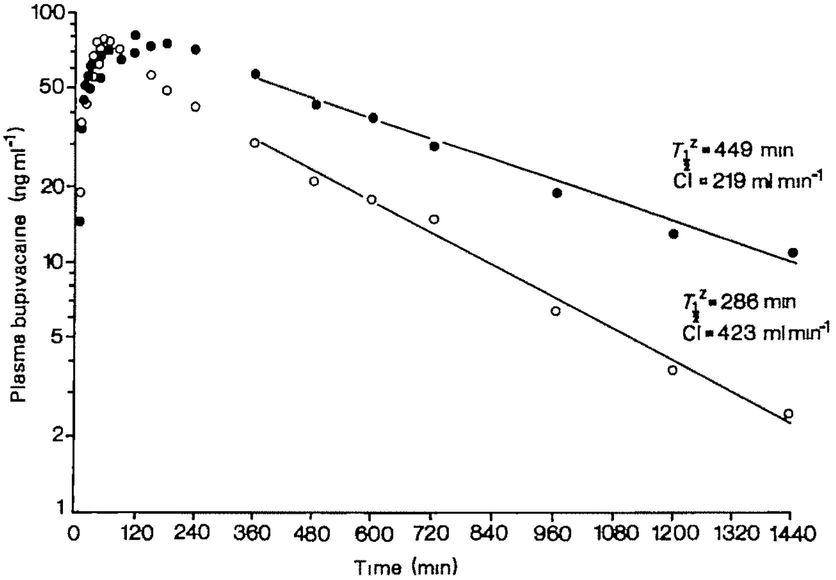

FIG. 3. Representative plasma concentration profiles after subarachnoid administration of hyperbaric 0.5% bupivacaine 3 ml in a patient of 64 yr (●——●) and one of 35 yr (○——○).

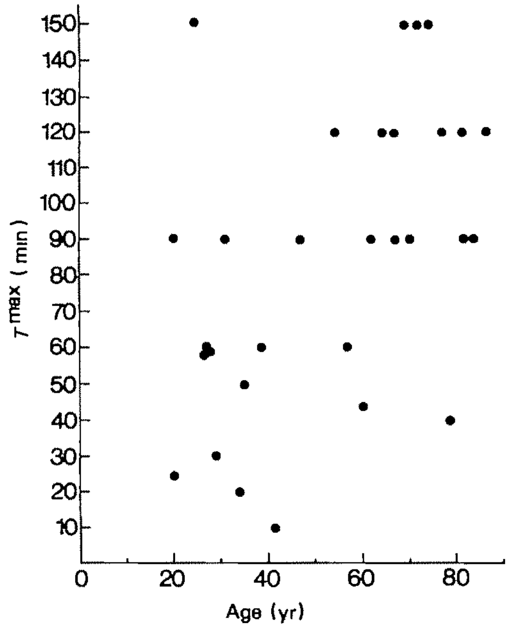

FIG. 4. Relationship between time to peak concentration of bupivacaine and age.

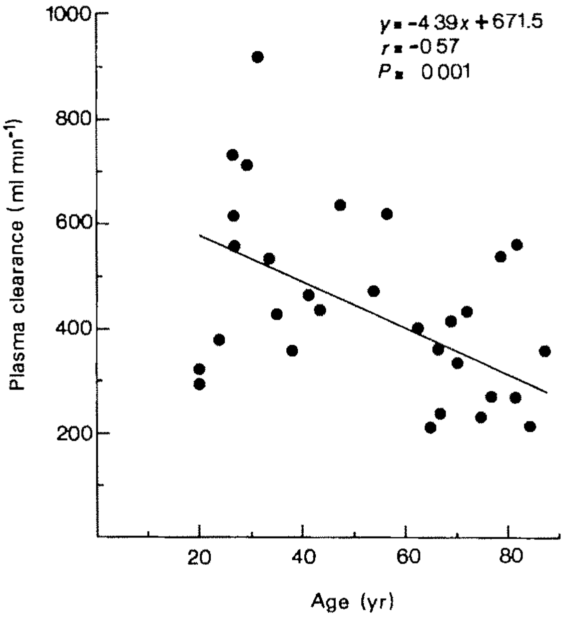

FIG. 5. Relationship between total plasma clearance and age.

Peak plasma concentrations of bupivacaine were similar in both groups, but the corresponding peak times were significantly longer in older patients. In addition, there was a moderate correlation between the time to peak concentration and age ($r_s = 0.55$, $P < 0.001$) (fig. 4). The terminal half-life was significantly prolonged ($P < 0.05$) and the total plasma clearance was significantly lower in the older patients ($P < 0.01$). There was a moderate inverse correlation between total plasma clearance and age ($r = -0.57$, $P < 0.001$) (fig. 5).

DISCUSSION

The most important clinical features of spinal anaesthesia are the height (level) and duration of sensory analgesia. Factors which influence the extent and duration of the neural blockade after subarachnoid administration of hyperbaric bupivacaine include the baricity of the solution [10, 13, 18–20], the position of the patient [21–23], the injected volume [24–27], and the concentration of the local anaesthetic in the solution [24, 26, 28]. This study shows that age is another factor.

Our results clearly demonstrate that, with hyperbaric bupivacaine solutions, ageing results in both a slightly higher level of analgesia, at the cost of an increase in the latency time to maximal spread, and a slightly faster onset of motor blockade. These changes are of minor clinical significance. It is not surprising that ageing alters the clinical profile of local anaesthetics: it results in a gradual degeneration of the central and peripheral nervous systems [1, 2], changes in the anatomical configuration of the lumbar and thoracic spine [29] and, possibly, a reduction of the volume of the CSF [30]. These alterations may all contribute to the increased spread of analgesia and the more rapid onset of motor blockade with a hyperbaric solution. In addition, the specific gravity of the CSF increases with age [31, 32], making the local anaesthetic solution less hyperbaric. This may decrease the spread of the solution. However, clinically, this effect is dominated by the factors just mentioned, which promote the spread of analgesia.

The results obtained in this study with hyperbaric bupivacaine solutions contrast with those, obtained by Park, Balingit and Macnamara [8] and Tuominen and colleagues [9] with hyperbaric amethocaine. However, both those studies [8, 9] used different volumes and techniques and therefore comparison with the present results is difficult. In well controlled studies in

TABLE IV. *Pharmacokinetic data obtained after subarachnoid administration of glucose-free 0.5% bupivacaine (from Veering and colleagues [6]) and hyperbaric 0.5% bupivacaine in 8% glucose (mean ± SD). *Statistical difference between group 1 and group 2 in that patient study.*

	Glucose-free 0.5% bupivacaine		Hyperbaric 0.5% bupivacaine		Effect of age	Effect of glucose
	Group 1 20–55 yr	Group 2 > 55 yr	Group 1 20–55 yr	Group 2 > 55 yr	(*P*)	(*P*)
C^{max} (min)	75±25	96±23*	71±28	75±23	0.062	0.049
T^{max} (min)	84±53	105±54	65±38	107±28*	0.008	0.47
$T_{\frac{1}{2}}^{z}$ (min)	288±64	270±93	334±64	427±138*	0.013	0.005
Cl (ml min^{-1})	461±94	284±74*	525±172	366±134*	< 0.001	0.024

younger patients, comparisons between hyperbaric solutions of amethocaine and bupivacaine revealed a quite similar action of both local anaesthetics [21, 28, 33, 34].

The marked prolongation of the duration of analgesia at the T12 dermatome in the older patients would allow more time for the performance of lower abdominal surgery in this group.

The results obtained in this study differ from those obtained by us in a previous study, concerning the influence of age after subarachnoid administration of glucose-free bupivacaine solutions [6]. Using glucose-free bupivacaine solutions we observed a significantly more rapid onset of analgesia at the caudal segments, no significant effect on the highest level of analgesia, and a marked prolongation of the total duration of analgesia with advancing age. Furthermore, the time to attain the maximum degree of motor blockade was significantly shorter in older patients. In fact, a glucose-free solution of 0.5% bupivacaine is slightly hypobaric (baricity at 37 °C, 0.9990), resulting in a one-segment further spread in patients who remain sitting for 2.5 min or longer after injection of the glucose-free solution compared with patients who remain sitting for 2 min after the injection [35]. Under clinical conditions the distribution of a glucose-free solution of 0.5% bupivacaine resembles that of isobaric solutions more than that of truly hypobaric solutions. As a result of the more restricted spread and, consequently, a higher drug concentration in the CSF, the effects of isobaric solutions always last much longer [36–38]. Furthermore, addition of glucose to the solution may alter the pharmacodynamic profile of the local anaesthetic, for example by altering the osmolality [35] or by interference with the absorption of the local anaesthetic from the subarachnoid space into the general circulation [14, 15, 39, 40].

The pharmacokinetic data obtained in this study also differ from those in the study with glucose-free bupivacaine solutions [6]. With hyperbaric solutions, ageing did not affect the peak plasma concentrations of bupivacaine, but did prolong the corresponding peak times and the terminal half-life. With glucose-free bupivacaine solutions, ageing increased the peak plasma concentration, but did not alter the peak time or terminal half-life. The difference in the results obtained with different bupivacaine solutions suggest that glucose interferes with the pharmacokinetics.

In order to distinguish between the effects of ageing and those of addition of glucose the data obtained in this study and the data obtained in the study with glucose-free bupivacaine solutions were re-analysed, using a two-way analysis of variance (table IV). This analysis confirmed the observations from the present study concerning the effects of age: ageing does not influence C^{max} of bupivacaine, but prolongs the corresponding T^{max} and $T_{\frac{1}{2}}^{z}$ and decreases Cl. In addition, the analysis demonstrated that addition of glucose decreases C^{max}, prolongs $T_{\frac{1}{2}}^{z}$ and increases Cl, but does not alter T^{max}. The effects of glucose on C^{max} and T^{max} differ from those reported by Axelsson and colleagues [14] and Burm and colleagues [15], who both found that glucose decreased T^{max} but did not alter C^{max}. This reason for this discrepancy remains unclear.

In conclusion, the present study demonstrates that advancing age alters both the neural blockade characteristics and the pharmacokinetics after subarachnoid administration of hyperbaric solutions of bupivacaine. The results clearly show an effect of ageing on the disposition, that is, the total plasma clearance of bupivacaine. The effect of ageing on the time at which the peak plasma concentration is obtained, suggests an effect on the initial absorption, but may also be the result of the decreased total plasma clearance. The effect on the terminal half-life, which in fact reflects a slow absorption half-life in younger patients [40], indicates that the late absorption proceeds more slowly in older patients. This slowing of the absorption is not accompanied by a prolongation of the duration of analgesia in the upper and lower dermatomes.

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POSTURE AND POST-SPINAL HEADACHE

A Controlled Trial in 80 Obstetric Patients

E. A. THORNBERRY AND T. A. THOMAS

SUMMARY

Eighty obstetric patients receiving subarachnoid anaesthesia for second and third stage procedures, excluding Caesarean section, were studied. They were randomly allocated post-partum to either 24 h bed rest or early (6 h post spinal) mobilization. Patients were followed up at 48 h post-partum and the incidence and severity of post-spinal headache noted. There was a significantly greater incidence of severe spinal headaches in the "bed-rest" group and three patients in this group required blood patch treatment for their headache. Early mobilization is, therefore, the recommended management after spinal anaesthesia for these types of obstetric procedure.

The reported incidence of post-spinal headache varies between 3 and 60%. It is higher in females, especially when they are pregnant. A period of recumbency was thought to reduce the incidence or severity of this headache, and 24 h horizontal bed rest was the standard post-spinal management for many years. Recently, this regimen has been questioned and several workers [1, 2] have suggested it is unnecessary in non-obstetric patients.

The purpose of this study was to establish whether bed rest was beneficial in preventing post-spinal headache in the particularly susceptible obstetric patient. At the same time, we noted difficulties with micturition or breast-feeding associated with the bed rest, since these factors significantly affect the overall comfort and satisfaction of the post-partum patient.

PATIENTS AND METHODS

Eighty obstetric patients receiving subarachnoid anaesthesia for second- and third-stage procedures (table I) were studied. They were randomly allocated to groups A and B by means of numbered envelopes containing a coded slip. Subarachnoid puncture was performed with a 25-gauge or a 26-gauge needle and anaesthesia produced with 1.2–1.6 ml of 1:200 cinchocaine in hyperbaric dextrose. All patients received at least 1500 ml of Hartmann's solution i.v. during the procedure and the subsequent 6-h bed rest, a minimum of 500 ml being given before the block. After delivery all patients were allowed free access to oral fluids. All patients were confined to bed for 6 h after delivery, the standard management in this hospital. Group A patients were then allowed to mobilize freely and were discouraged from staying in bed unless they had symptoms of a headache. Group B patients were kept horizontal in bed for a total of 24 h. The accuracy of post-partum fluid balance recordings was poor and they are not reported here.

TABLE I. *Age, parity and obstetric procedures undertaken in groups A and B*

	Group A (Ambulant)	Group B (Bed-rested)
Age (yr)	28 (21–39)	28 (19–39)
Primiparous	13	16
Multiparous	28	23
Retained placenta products of conception	26	25
Vaginal haematoma evacuation and suturing	14	13
Forceps delivery	1	1

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Approximately 48 h after the subarachnoid block was performed the patients were visited and details of any headache, problems with micturition or breast-feeding were recorded. A spinal headache was defined as one which increased in intensity in the upright posture and was relieved by lying down. The spinal headache was arbitrarily defined as "severe" when the patient described it as such and was obviously distressed, or if it was debilitating, persistent and associated with additional neurological symptoms such as neck stiffness, blurred vision or tinnitus.

Statistics

Differences between the groups were analysed using a chi-squared test with Yates' correction for small numbers. Fisher's exact test was used for comparisons of the incidence of severe headache, blood patch and difficulty with breast-feeding.

RESULTS

Group A comprised 41 patients and group B 39 patients. There were no significant differences between the groups in respect of age, parity or type of obstetric procedure undertaken (table I).

The incidences of headache, and of problems with micturition or breast feeding or both (in both groups) are shown in table II.

"Spinal" headaches occurred in 9 group A patients and in 36% of the patients in group B. There were insignificant differences between the groups in the incidence of mild spinal headache, difficulty with micturition and difficulty with breast-feeding. The incidence of severe spinal headache, however, was significantly greater ($P < 0.025$) in the bed-rested patients (group B), in three of whom the headaches were severe enough to require management using a blood patch.

TABLE II. *Incidence of post-spinal sequelae in patients in groups A and B with significance of difference*

	Group A (Ambulant)	Group B (Bed-rested)	P
Number in group	41	39	ns
Spinal headache	9	14	ns
Severe spinal headache	1	8	0.025
Blood patch	0	3	ns
Difficulty with micturition	12	19	ns
Number breast-feeding	31	31	ns
Difficulty breast-feeding	6	10	ns

DISCUSSION

Post-spinal headache was first documented by August Bier. Following subarachnoid injection of cocaine in 1889, he reported a severe headache, which was exacerbated by sitting or standing, and was relieved by lying down. The cause of this type of postural headache still remains in doubt nearly 90 years later. It is widely assumed that loss of CSF via the dural puncture site is responsible and a loss of 30–50 ml has been reported [3] to cause a headache. The reduction of intradural volume of CSF is said to allow cranial meninges to move in relation to surrounding bony structures and results in traction on communicating blood vessels and nerves [4]. This explanation is not totally convincing in the face of the rapidity of cure following the more recent introduction of blood patching for troublesome spinal headache, but is the basis of most prophylactic regimens. Brocker [5] showed a reduction in the incidence of headache from 36.5% to 0.5% by placing patients in the prone position for 3 h following diagnostic lumbar puncture. He suggested that this management reduced the CSF loss by reducing hydrostatic pressure at the puncture site. He also postulated that, in addition to keeping the puncture site uppermost, this position caused the dura to slide over the arachnoid and, therefore, the two puncture sites were no longer in alignment, effectively closing the defect. However, Handler and colleagues [6] failed to confirm his results and questioned his anatomical explanation. Other prophylactic regimens have attempted to reduce CSF loss by increasing the pressure within the extradural space with the application of abdominal binders [7] and by the extradural infusion of physiological saline [8]. An increased rate of CSF production has been sought by improving hydration with i.v. infusion [9] or antidiuretic therapy [10].

Prophylactic systemic analgesia has in general, been ineffective. However, Kaukinen and associates [11] have shown that indomethacin 100 mg (as a suppository) given 6 h after the puncture reduced the incidence of post-spinal headache compared with a control group. However, the most convincing method to reduce the incidence of post-spinal headache is the use of small, 25-gauge or 26-gauge, spinal needles. Tourtellotte and colleagues [12] decreased the incidence from 36% with 22-gauge needles to 12% with 26-gauge needles. In females the incidence decreased from 40% to 13%—a significant improvement.

Earlier prophylactic regimens have included a high fluid intake and bed rest in the horizontal position. This form of management had become traditional until recent studies in patients after lumbar puncture or spinal anaesthesia suggested that bed rest, although useful in treating spinal headache, contributed little to a reduction in the incidence of the problem.

Unfortunately, it was not possible to identify accurately any difference in fluid intake between the groups in our study because of inadequate charting of post-partum fluid balance. It is possible that the ambulant patients drank more because their mobility gave them better access to fluids, but we believe that the difference of intake was small because all patients were encouraged to drink 3–4 litre for the first day post-partum. Nevertheless, this possibility must of itself make an ambulant regimen preferable.

Enforced bed rest in the early post-partum period is a great inconvenience to nursing mothers. Difficulty with micturition, common in the post-partum period, is exacerbated by the supine position. Breast feeding becomes difficult, or impossible, and the frustration and anger expressed by some "bed-rested" mothers could adversely affect mother–baby bonding. One patient withdrew from this study rather than continue trying to breast-feed in the horizontal position. Once established, a severe spinal headache consigns the mother to further bed rest, more inconvenience and interference with the establishment of breast-feeding and mother–baby bonding. Some cases are so severe or protracted that blood patching is necessary. Any treatment regimen that reduces the incidence of severe post-spinal headache in these patients must therefore be of great value.

Our results confirm the overall high incidence of post-spinal headache in obstetric patients who are bed rested for 24 h following subarachnoid anaesthesia. In patients in this study who were allowed out of bed 6 h after subarachnoid blockade, the overall incidence of severe post-spinal headache was lower. We have not confirmed the association between headache and needle size, in bed-rested or ambulant patients. If adequate numbers of patients in whom a 26-gauge needle was used had been available, a difference in favour of 26-gauge needles might have emerged in the bed-rested group of patients. This would then confirm the advantage of the smaller needle, but only in bed-rested patients.

The results of this study indicate that prophylactic post-spinal bed rest actually increases the likelihood of severe post-spinal headache, and we believe that there is now good evidence to show that the institution of bed rest should be abandoned as prophylaxis against spinal headache following subarachnoid block for second- and third-stage procedures in obstetric patients.

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EFFECTS OF ALTERED PATTERNS OF VENTILATION AND OF INCREASED CARDIAC OUTPUT ON BLOOD FLOW TO A COLLAPSED LUNG IN ANAESTHETIZED, CLOSED-CHEST DOGS

D. J. NIBLETT, D. CANNON AND M. K. SYKES

SUMMARY

Right-to-left shunt ($\dot{Q}s/\dot{Q}t$) was measured by the SF_6 and oxygen methods in 13 anaesthetized closed-chest dogs intubated with a double-lumen endobronchial tube. Collapse of the left lung increased $\dot{Q}s/\dot{Q}t$ from 10% to 23%, suggesting that blood flow to the left lung had been reduced by about 60%. Increasing right lung mean airway pressure by the alteration of the inspiratory:expiratory time ratio or the application of PEEP produced a small but non-significant increase in $\dot{Q}s/\dot{Q}t$ with significant increases in arterial and mixed venous carbon dioxide tensions, and arterial to right lung end-tidal carbon dioxide tension difference. Fluid loading during collapse increased cardiac output and pulmonary vascular pressures, but $\dot{Q}s/\dot{Q}t$ did not differ significantly from the normovolaemic collapsed state. Increasing the right mean airway pressure in this condition had no effect on $\dot{Q}s/\dot{Q}t$ or carbon dioxide tensions.

The major cause of a reduction in blood flow through an underventilated area of lung is hypoxic pulmonary vasoconstriction (HPV), but in collapsed areas of lung this mechanism may be augmented by the increase in $P\text{CO}_2$ resulting from the equilibration of the lung with mixed venous blood [1]. In most patients with acute lung disease the application of a positive end-expiratory pressure (PEEP) re-expands collapsed alveoli and so decreases intrapulmonary shunt ($\dot{Q}s/\dot{Q}t$). However, in some patients, particularly those with predominantly unilateral lung disease, PEEP may have the opposite effect [2–6]. There is evidence that the increase in $\dot{Q}s/\dot{Q}t$ is associated with an increase in blood flow to the damaged lung [7] and it is believed that the redistribution of flow results from the increase in pulmonary artery pressure produced by compression of the pulmonary capillaries in the ventilated alveoli. This increases the driving pressure across the areas of lung not exposed to this pressure and so increases $\dot{Q}s/\dot{Q}t$ [8–10].

There is experimental evidence that an increase in the mean airway pressure ($P_{\overline{aw}}$) applied to a ventilated lung can shift blood flow to a collapsed lung in dogs with a closed chest [11] or to a collapsed left lower lobe in dogs with an open chest [12, 13]. However, in a recent series of investigations in dogs with an open chest an increase in $P_{\overline{aw}}$, produced by the application of PEEP or an increase in inspiratory:expiratory (I:E) time ratio, failed to alter the distribution of blood flow from the ventilated right lung to the left lower lobe when the latter was insufflated with oxygen, 7% oxygen in nitrogen, or subjected to collapse [14]. Since the redistribution of flow from a collapsed area of lung is less when the chest is closed than when it is open [15–17], we decided to repeat the studies in a closed-chest preparation with normal and increased blood volume, using measurements of right-to-left shunt as an index of flow through the collapsed lung.

MATERIALS AND METHODS

Thirteen mongrel dogs (17–29 kg) were anaesthetized with thiopentone $30\ \text{mg kg}^{-1}$ following premedication with Hypnorm (fentanyl citrate

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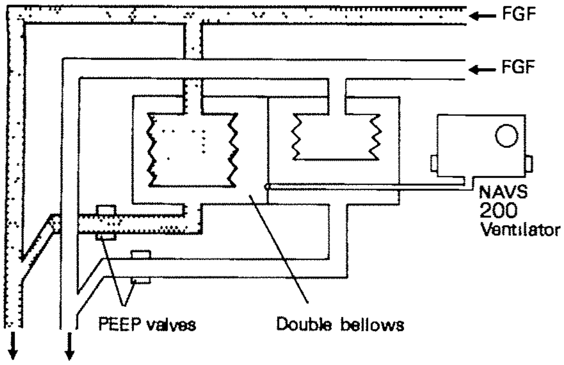

FIG. 1. Diagram of the system used to provide independent ventilation of the right and left lung. Expired gas passed through the PEEP valves to the chamber surrounding the bellows and thence to the expiratory port on the ventilator. FGF = Fresh gas flow.

0.315 mg ml^{-1} and fluanisone 10 mg^{-1}; Janssen) i.m. in a dose of 0.06 ml kg^{-1}. After tracheal intubation with a 10-mm i.d. cuffed plastic tube, the lungs were ventilated with the right-hand side of the double bellows-in-box system (fig. 1) at 10 b.p.m., the tidal volume being adjusted to give an end-tidal carbon dioxide concentration of 4.5–5%. Anaesthesia was maintained with 1.5% halothane in oxygen during surgery and, thereafter, with a continuous infusion of Hypnorm 0.13 ml kg^{-1} h^{-1} plus 0.2–0.5% halothane to the right lung. The dogs remained in the supine position throughout the study. Blood loss was replaced by the infusion of Haemaccel (Hoechst, U.K., Ltd) and any non-respiratory acidosis corrected by the infusion of 8.4% sodium bicarbonate to maintain a base excess of 0 ± (SD) 2.0 mmol litre^{-1}. A carotid arterial cannula was inserted to permit the measurement of arterial pressure, blood-gas tensions and haematocrit. The ECG and oesophageal temperature were monitored throughout.

A Swan–Ganz catheter was introduced via the right external jugular vein for measurement of pulmonary artery pressure (P_{PA}), pulmonary capillary wedge pressure (PCWP) and for the sampling of mixed venous blood. Catheters in the left external jugular vein and femoral artery were used for cardiac output estimations by dye dilution, and a saline solution equilibrated with 20% sulphur hexafluoride (SF_6) in nitrogen was infused continuously to a femoral vein for the measurement of intrapulmonary shunt.

Tracheotomy was performed and one limb of a double-lumen endobronchial tube (35-French gauge National Catheter Corp.) introduced to the left main bronchus, whilst airway pressure was monitored to confirm correct positioning. Separation of the two sides was confirmed by pressurizing the right limb of the tube whilst the left was connected to an under-water seal. The two limbs of the tube were then connected to the two bellows-in-box systems and tidal volumes adjusted to produce equal end-tidal carbon dioxide concentrations on each side. The values of PEEP were then adjusted to match the mean airway pressures. The second stage bellows were compressed by a Nuffield AVS 200 ventilator (Penlon Ltd, Abingdon) which had been modified to provide an extended range of inspiratory times. The efficiency of the ventilator circuit was checked before use on a model lung.

Design of study

The study consisted of 10 stages, a set of cardiovascular and respiratory measurements being taken at each stage with a right lung $F_{I_{O_2}}$ of 1.0. During the first stage (1), both lungs were ventilated with an $F_{I_{O_2}}$ of 1.0 with an inspiratory:expiratory (I:E) time ratio of 1:2. The left lung was then collapsed by occluding the left endobronchial tube, and 30 min later a second set of measurements was obtained (2). Further sets of measurements were made as follows: (3) during ventilation of the right lung with an I:E ratio of 2:1; (4) with an I:E ratio of 1:2, but with positive end-expiratory pressure added to produce the same mean airway pressure ($P_{\overline{aw}}$) as the 2:1 ratio; (5) with an I:E ratio of 1:2 but with PEEP increased to double the $P_{\overline{aw}}$ (fig. 2). The collapsed lung was then re-expanded and ventilated with oxygen to provide a second control measurement (6). Thereafter, left lung collapse was re-instituted and Haemaccel infused to increase PCWP to 16–20 mm Hg. A set of measurements was then obtained with each of the four conditions of ventilation outlined above, a period of 30 min being allowed for stabilization between successive readings (7–10). The position of the endobronchial tube and the area of collapse were confirmed at autopsy in all animals.

Changes in the perfusion of the collapsed area of lung were estimated by shunt measurements using both oxygen and SF_6 methods. The oxygen shunt ($\dot{Q}s/\dot{Q}t_{O_2}$) was calculated from the following equation:

$$\dot{Q}s/\dot{Q}t_{O_2} = \frac{(Cc'_{O_2} - Ca_{O_2})}{(Cc'_{O_2} - Ca_{O_2}) + (Ca_{O_2} - C\bar{v}_{O_2})}$$

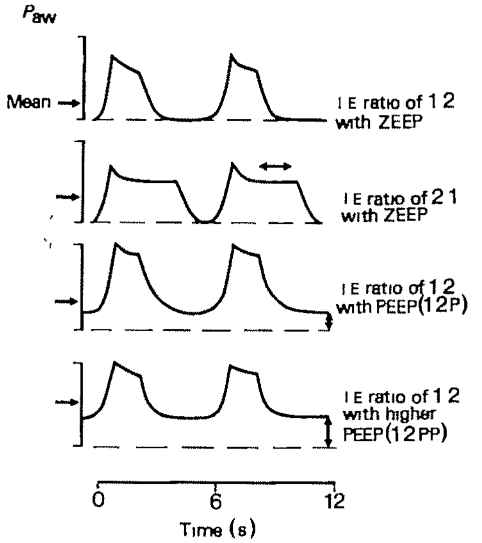

FIG. 2. Airway pressure patterns (P_{aw}) applied to the right lung. From above down I:E ratio 1:2, 2:1, with zero end-expiratory pressure (ZEEP), and 1:2+PEEP. With the fourth pattern, 1:2+PP, PEEP was increased to give a $P_{\overline{aw}}$ double that recorded with 2:1 and 1:2+P.

The end-pulmonary capillary-to-arterial oxygen content difference ($Cc'_{O_2}-Ca_{O_2}$) was calculated from the oxygen saturation derived from the Severinghaus nomogram [18], the haemoglobin (measured by the cyanmethaemoglobin technique) and a combining factor of 1.39. The end-pulmonary capillary PO_2 was assumed to equal alveolar PO_2 (PA_{O_2}) and was calculated from the simplified alveolar air equation:

$$PA_{O_2} = PI_{O_2} - \frac{Pa_{CO_2}}{0.8}$$

whilst the arterial-to-mixed venous oxygen content difference ($Ca_{O_2}-Cv_{O_2}$) was measured directly with a Lex-O_2-Con analyser, thus minimizing errors from variations in the oxygen dissociation curve.

The SF_6 shunt ($\dot{Q}s/\dot{Q}t_{SF_6}$) was calculated from the ratio of arterial to mixed venous SF_6 contents [19]. Synchronous 5-ml samples of arterial and mixed venous blood were taken in duplicate into heparinized glass syringes, and then equilibrated at 20 °C with 20 ml of 100% nitrogen at atmospheric pressure for 30 min. The supernatant gas was analysed in 5-ml aliquots using an electron capture detector on a Perkin-Elmer Sigma 3B chromatograph. By using suitable carrier gas flows, sharp peaks of SF_6 distinct from those of oxygen could be recorded, the peak heights being proportional to the concentration of SF_6 in each sample.

Cardiac output was measured ($\dot{Q}t$) (dye dilution) by injecting cardio-green (Sigma Chemicals Ltd) to the pulmonary artery, the area under the curve recorded by a CO-10R cardiac output monitor (Waters Instruments Inc.), $\dot{Q}t$ being calculated from the formula:

$$\dot{Q}t = \frac{\text{amount of dye (mg)} \times 60 \times 0.856}{\text{peak height of curve} \times \text{width at } \tfrac{1}{2} \text{ peak height} \times 100} \times \text{calibration factor}$$

The coefficient of variation of duplicate estimations was less than 7%.

Statistical analysis

Each of the recorded variables was analysed using the two-way analysis of variance. Comparison of individual stages was by Student's *t* test at the 5% level. Related comparisons were grouped and the required level of significance adjusted for the number of comparisons using Sidak's inequality [20]. The reduction in the number of comparisons in the later stages of the study was the result of technical problems and other local difficulties which prevented completion of the full experimental programme.

RESULTS

The only significant difference between the two control stages was that mixed venous oxygen tension (Pv_{O_2}) was lower at stage 6 than stage 1 (table I). Collapse of the left lung resulted in a reduction in arterial PO_2, an increase in both SF_6 and oxygen shunts, and a reduction in mean carotid arterial pressure ($P_{\overline{CA}}$) (table II). Increasing right mean airway pressure ($P_{\overline{raw}}$) from 4.5 to 13.1 mm Hg during collapse had no effect on $\dot{Q}s/\dot{Q}t_{SF_6}$ (fig. 3), but increased mean pulmonary artery pressure ($P_{\overline{PA}}$), and arterial and mixed venous PCO_2 (Pa_{CO_2}, Pv_{CO_2}), the values during the high value of PEEP (stage 5) being significantly higher than those during stage 2. The arterial-to-right lung end-tidal PCO_2 difference also increased from 0.7 kPa at stage 2 to 1.4 kPa at stage 5.

Fluid loading by the infusion of Haemaccel 1–2 litre over a period of 15–20 min (stages 7–10)

TABLE I. *Blood-gas tensions; right end-tidal* P_{CO_2} ($P\acute{E}_{CO_2}$) *and arterial to end-tidal* P_{CO_2} *differences* ($Pa_{CO_2}-P\acute{E}_{CO_2}$) *at each stage of the experiment (mean ± SEM). V = ventilation; C = collapse; FL = Fluid loading. Right lung conditions:* I:E *ratio: P and PP signify PEEP at two different values.* n = *Number of observations.* * *Significant differences* ($P < 0.05$) *between stages shown in parentheses*

Stage	Lung conditions Left	Lung conditions Right	*n*	Pa_{O_2} (kPa)	Pa_{CO_2} (kPa)	$P\bar{v}_{O_2}$ (kPa)	$P\bar{v}_{CO_2}$ (kPa)	$P\acute{E}_{CO_2}$ (kPa)	($Pa_{CO_2}-P\acute{E}_{CO_2}$) (kPa)
1	V 100% O_2	1:2	13	61.8±2.9	4.3±0.1	7.5±0.3	5.4±0.2	3.9± 0.2	0.3±0.2
2	C	1:2	13	26.9±2.4* (1, 6)	5.0±0.2	6.5±0.3	6.0±0.2	4.3±0.2	0.7±0.2
3	C	2:1	13	28.9±2.4* (1, 6)	5.8±0.2* (1, 6)	6.0±0.3* (1)	6.9±0.2* (1)	4.9±0.2* (1, 6)	1.0±0.2
4	C	1:2P	12	23.5±2.6* (1, 6)	5.7±0.2* (1, 6)	6.1±0.3* (1)	7.0±0.2* (1, 6)	4.9±0.3* (1, 6)	0.9±0.2
5	C	1:2PP	11	23.3±2.5* (1, 6)	6.6±0.2* (1, 2, 6)	6.2±0.3* (1)	7.6±0.2* (1, 2, 6, 7)	5.3±0.3* (1, 2, 6)	1.4±0.2* (1)
6	V 100% O_2	1:2	11	65.6±3.1	4.3±0.2	6.4±0.4* (1)	5.5±0.2	3.9±0.2	0.4±0.2
7	C+FL	1:2	10	35.9±2.6* (1, 6)	5.2±0.2	6.6±0.3	5.8±0.2	4.4±0.3	0.7±0.3
8	C+FL	2:1	9	28.3±3.0* (1, 6)	5.6±0.3* (1, 6)	6.2±0.3	6.2±0.3	5.0±0.3	0.6±0.3
9	C+FL	1:2P	9	32.7±3.0* (1, 6)	5.6±0.3* (1, 6)	6.4±0.3	6.2±0.3	5.0±0.3	0.7±0.3
10	C+FL	1:2PP	8	35.2±3.6* (1, 6)	5.9±0.3* (1, 6)	6.9±0.4	6.5±0.3	5.9±0.3* (1, 2, 6, 7)	0.0±0.3* (5)

TABLE II. *Shunt as measured by* SF_6 ($\dot{Q}s/\dot{Q}t_{SF_6}$) *and oxygen* ($\dot{Q}s/\dot{Q}t_{O_2}$) *techniques, cardiac output* ($\dot{Q}t$), *mean pulmonary artery* ($P_{\overline{PA}}$) *and pulmonary capillary wedge (PCWP) pressures, mean carotid artery pressure* ($P_{\overline{CA}}$), *right lung mean* ($P_{\overline{raw}}$), *peak (peak* P_{raw}), *and end-expiratory (rPEEP) pressures for each stage of the experiment (mean ± SEM). V = Ventilation; C = collapse; FL = Fluid loading. Right lung conditions:* I:E *ratio: P and PP signify PEEP at two different values.* n = *number of observations.* **Significant differences* ($P < 0.05$) *between stages shown in parentheses*

Stage	Lung conditions Left	Lung conditions Right	*n*	$\dot{Q}s/\dot{Q}t_{SF_6}$ (%)	$\dot{Q}s/\dot{Q}t_{O_2}$ (%)	$\dot{Q}t$ (litre min^{-1})	$P_{\overline{PA}}$ (mm Hg)	PCWP (mm Hg)	$P_{\overline{CA}}$ (mm Hg)	$P_{\overline{raw}}$ (mm Hg)	peak P_{raw} (mm Hg)	r PEEP (mm Hg)
1	V 100% O_2	1:2	13	10.1 ±1.4	12.3 ±1.4	2.4 ±0.2	13.4 ±0.6	5.8 ±0.8	110.4 ±6.7	4.9 ±0.1	17.8 ±1.3	0.9 ±0.1
2	C	1:2	13	23.0 ±2.5* (1, 6)	23.4 ±2.0* (1, 6)	2.1 ±0.2	13.2 ±1.2	5.8 ±1.2	83.5 ±3.7* (1, 6)	4.5 ±0.3	18.4 ±1.2	0.5 ±0.3
3	C	2:1	13	23.9 ±2.6* (1, 6)	21.0 ±2.0* (1, 6)	1.9 ±0.2	15.0 ±1.2	5.3 ±1.3	82.0 ±3.7* (1, 6)	7.4 ±0.3* (1, 2, 6)	17.6 ±1.2	1.1 ±0.3
4	C	1:2P	12	26.2 ±2.7* (1, 6)	23.6 ±2.1* (1, 6)	2.0 ±0.2	16.6 ±1.2	6.1 ±1.2	86.8 ±3.7* (1, 6)	7.5 ±0.4* (1, 2, 6)	19.9 ±1.2	3.3 ±0.3* (1–3, 6)
5	C	1:2PP	11	28.9 ±2.8* (1, 6)	27.4 ±2.1* (1, 6	2.0 ±0.2* (1)	23.3 ±1.2* (1–4, 6)	8.2 ±1.2	78.7 ±3.9* (1, 6)	13.1 ±0.4* (1–4, 6)	24.7 ±1.2* (1, 4, 6)	9.4 ±0.3* (1–4, 6)
6	V 100% O_2	1:2	11	5.6 ±1.7	8.5 ±1.6	2.2 ±0.2	16.0 ±0.7	7.5 ±1.0	104.2 ±3.9	4.7 ±0.1	15.4 ±1.4	0.2 ±0.1
7	C+FL	1:2	10	26.9 ±3.0* (1, 6)	26.4 ±2.4* (1, 6)	4.1 ±0.3* (2–6)	30.0 ±1.4* (1–6)	19.0 ±1.4* (1–6)	117.7 ±4.3* (2)	5.3 ±0.4	18.1 ±1.3	0.5 ±0.3
8	C+FL	2:1	9	32.3 ±3.2* (1, 6)	32.2 ±2.5* (1, 2, 6)	4.0 ±0.3* (2–6)	31.6 ±1.5* (1–6)	19.5 ±1.6* (1–6)	110.6 ±4.6* (3)	9.0 ±0.4* (6, 7)	18.9 ±1.4	0.7 ±0.3
9	C+FL	1:2P	9	28.9 ±3.2* (1, 6)	30.2 ±2.5* (1, 6)	4.5 ±0.3* (2–6)	33.7 ±1.5* (1–6)	20.6 ±1.5* (1–6)	112.5 ±4.6* (4)	8.9 ±0.4* (6, 7)	22.2 ±1.4	4.0 ±0.3* (6–8)
10	C+FL	1:2PP	8	26.8 ±3.4* (1, 6)	28.5 ±2.6* (1, 6)	4.3 ±0.3* (2–6)	33.0 ±1.7* (1–6)	23.9 ±1.6* (1–6)	100.4 ±4.9* (5)	13.7 ±0.4* (6–9)	25.8 ±1.5* (6–8)	9.5 ±0.4* (6–9)

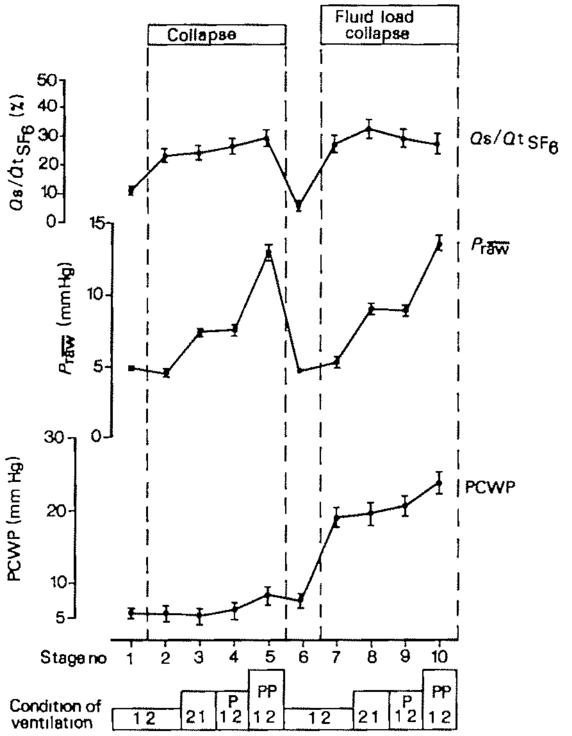

FIG. 3. Means ± SEM for SF_6 shunt, right mean airway pressure ($P_{\overline{raw}}$) and pulmonary capillary wedge pressure (PCWP) at each stage of the experiment. Ventilatory patterns indicated below abscissa as in text.

doubled cardiac output and produced significant increases in $P_{\overline{PA}}$ and mean pulmonary capillary wedge pressure (PCWP), but no significant change in $P\bar{v}_{O_2}$ or $P\bar{v}_{CO_2}$. $\dot{Q}s/\dot{Q}t_{O_2}$ at stage 8 was significantly higher than at stage 2, but otherwise there were no differences in Pa_{O_2} and $\dot{Q}s/\dot{Q}t$ after transfusion. There were no significant changes in these measurements or in Pa_{CO_2}, $P\bar{v}_{CO_2}$, $P\bar{v}_{O_2}$, $P_{\overline{PA}}$, PCWP or $\dot{Q}t$ in response to the application of different patterns of ventilation to the right lung. There were no significant changes in pH which remained within the limits 7.34 ± (SD) 0.06 throughout the experiment. Complete collapse of the left lung was confirmed at autopsy in all animals and a little oedema was present in the dependent regions of both the left and right lungs in four dogs.

DISCUSSION

These results show that there was a significant increase in right-to-left shunt after the induction of left lung collapse, but that the percentage shunt was not altered by changes in the pattern of ventilation applied to the right lung. Fluid loading to a degree which resulted in significant increases in cardiac output and pulmonary vascular pressures during left lung collapse did not alter the percentage shunt. Subsequent changes in the pattern of right lung ventilation during the period of fluid loading also failed to alter the shunt.

The use of shunt measurements to provide an estimate of regional perfusion in the closed-chest preparation is dependent on a number of assumptions. The first is that the shunt measured in the control period during ventilation with an $F\text{I}_{O_2}$ of 1.0, is equally distributed between the two lungs so that there is a shunt of approximately 5% in each. The second assumption is that the right lung shunt is not affected by collapse of the left lung or by subsequent alterations in the right lung airway pressure. This assumption is probably not justified because the right lung transpulmonary pressure would have been increased by the application of PEEP and by the greater subatmospheric pleural pressure resulting from the collapse of the left lung [15,21], and this would have tended to reduce dependent zone collapse in the lung subjected to PEEP. If the shunt in the right lung had been reduced by the increased transpulmonary pressure, the actual increase in left lung blood flow in response to increased right airway pressure would have been greater than the measured increase in shunt, thus accentuating the trend observed in the shunt measurements. The third assumption is that the measured shunt does not include extrapulmonary sources of shunt. It is known that the oxygen method measures total right-to-left shunt from both intra- and extrapulmonary sources. However, the SF_6 shunt measures only intrapulmonary sources of shunt resulting from alveoli with a $\dot{V}\text{A}/\dot{Q}$ ratio of less than 0.05 [19]. The oxygen shunt values should, therefore, have been higher than the SF_6 shunt values throughout the investigation. However, although there was a good correlation between the two measurements (fig. 4), SF_6 shunts were consistently higher than the oxygen shunts, and the difference increased at higher shunt values.

There are a number of possible causes for this discrepancy. One is that the mixed venous SF_6 values may have been over-estimated as a result of non-linearity of the electron capture detector. However, care had been taken to assess the linearity of the analytical system before the

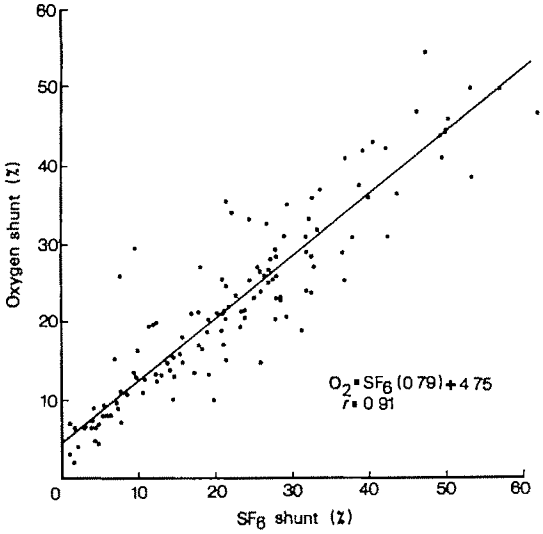

FIG. 4. Correlation between $\dot{Q}s/\dot{Q}t$ measured by the SF_6 and oxygen methods.

measurements were performed, and all the samples analysed in this study were well within the linear range of the electron capture detector. A second possible cause is under-estimation of Pa_{O_2} as a result of non-linearity of the oxygen electrode, the use of an inappropriate blood-gas factor or delay in sample analysis. It is believed that these sources of error had been eliminated by immediate analysis of blood samples and by the application of correction factors for non-linearity of the oxygen electrode and the blood-gas difference, a factor of 1.4 for the latter having been determined by tonometry of blood with high oxygen mixtures. A third possible cause is the loss of SF_6 into gas-containing alveoli in the collapsed lung or loss from the lung itself. This seems unlikely because the collapsed lung appeared to be completely airless at autopsy. The infusion of SF_6 was continued throughout the experiment and equilibrium should, therefore, have been reached between mixed venous blood and any gas-containing alveoli before the measurement was made. Complete separation of the lungs was repeatedly confirmed throughout the procedure and it seems unlikely that SF_6 could have diffused into the left main bronchus when the lung was collapsed. Whatever the cause of the discrepancy between the two methods, the results revealed similar directional changes, thus suggesting that extrapulmonary sources of shunt were little changed.

The onset of HPV in response to collapse of the left lung resulted in a biphasic reduction in arterial Po_2. This reached its lowest value 5–10 min after clamping the endobronchial tube and increased to a plateau value 20–30 min after initiating the collapse. Presumably, the initial decrease in Pa_{O_2} was associated with the decrease in alveolar Po_2 as the oxygen in the alveoli was consumed, whilst the secondary increase in Pa_{O_2} was caused by the reduction in blood flow to the collapsed lung caused by HPV.

If it is assumed that the initial shunt during bilateral oxygen ventilation (10%) was equally divided between the two lungs, and that the 5% shunt in the right lung was not changed by the onset of collapse in the left lung, then the contribution of the left lung collapse to the total shunt (stage 2) would have been $23-5 = 18\%$. Since 45% of the total pulmonary blood flow is normally distributed to the left lung of a dog [22, 23], this would represent a reduction in left lung flow of $(45-18)/45 = 60\%$, a value which is close to the 61–66% reduction in flow previously observed during lobar collapse in open-chest animals in this laboratory [1, 14, 24]. This suggests that these animals had an active HPV response.

There are three factors which may affect the diversion of flow in such a preparation. First, the magnitude of flow diversion in response to hypoxia is inversely related to the volume of lung made hypoxic [25], so that whole lung collapse in the closed-chest animals should produce a smaller proportional reduction in flow and, consequently, a relatively higher $\dot{Q}s/\dot{Q}t$, than lobar collapse in the open-chest animals. Second, collapse of a segment of lung in the closed-chest animal results in a greater numerical value of subatmospheric pressure over the collapsed segment. This increases the transmural pressure difference which tends to expand the extra-alveolar vessels, with a consequent reduction in regional pulmonary vascular resistance [17, 26, 27]. Furthermore, the reduction in left lung volume results in a reduction in intrapleural pressure which may increase the transpulmonary pressure across the ventilated right lung and so decrease vascular conductance at capillary level in this lung, thus also tending to increase $\dot{Q}s/\dot{Q}t$ [21]. The third factor is that in the closed chest, transmural filling pressures and cardiac output are greater than in the open-chest preparation. Since the cardiac output in the normovolaemic state was about 2.2 litre min^{-1} in the present experiments, and approximately 1.4 litre min^{-1} in previous open-chest experiments [14], this should have maintained a higher blood flow to the ventilated lung and so tended to reduce $\dot{Q}s/\dot{Q}t$. Since both Takaro [11] and Benumof and colleagues [12] observed decreases in hypoxic lung flow in the region of 36% in the closed-chest preparation, it seems reasonable to conclude that there must have been a substantial increase in vascular tone in the collapsed lung during the present investigations.

In previous studies there have been variable changes in the distribution of pulmonary blood flow in response to unilateral changes in $P_{\overline{aw}}$. Thus Sanchez de Leon and colleagues [13] found that the application of 10 cm H_2O PEEP to the ventilated lung increased the lobar to total blood flow ratio ($\dot{Q}l/\dot{Q}t$) from 8 to 15% during left lower lobe collapse in dogs with an open chest, whilst Benumof and co-workers [12] reported that an increase in PEEP to the ventilated lung from 2 to 10 cm H_2O resulted in an increase in $\dot{Q}l/\dot{Q}t$ from 10 to 23% when the chest was open and from 10 to 12% when the chest was closed. Takaro [11] demonstrated an increased flow to a hypoxic–hypercarbic lung when a constant pressure difference of 15 or 25 cm H_2O was applied for 20 s to the opposite hyperoxic lung. These results contrast with our previous open-chest studies which showed no increase in $\dot{Q}l/\dot{Q}t$ in response to increases in $P_{\overline{aw}}$ of 3–4 mm Hg produced by the addition of PEEP or change in I:E ratio, and with the present studies when even greater changes in $P_{\overline{aw}}$ failed to produce a change in $\dot{Q}s/\dot{Q}t$ during unilateral collapse in the closed chest.

There are a number of possible causes for the lack of change in the present studies. First, the increase in $P_{\overline{aw}}$ may have been less than that applied in other studies. Our increases in $P_{\overline{aw}}$ (4.5 to 7.4 to 13.1 mm Hg) were similar to the changes produced by increasing PEEP from 2 to 10 cm H_2O [12, 13], but less than the 15 and 25 cm H_2O difference in pressure between the two lungs applied by Takaro [11]. Benumof and co-workers [12] found that the change in $\dot{Q}l/\dot{Q}t$ was much less in the closed-chest group ($\dot{Q}l/\dot{Q}t$ 9.5–12.3%) and in our studies such a shift of flow could have been concealed by a reduction in $\dot{Q}s/\dot{Q}t$ in the ventilated lung in response to the increase in $P_{\overline{aw}}$. A second possibility is that the HPV response may have been stronger in our investigations than in those reported by other authors. In the experiments reported by Takaro [11], a 5% oxygen–5% carbon dioxide–90% nitrogen mixture was used to produce HPV in one lung, and this resulted in a 36% reduction of $\dot{Q}l/\dot{Q}t$, the increase in $\dot{Q}s/\dot{Q}t$ in response to hypoxia being from 15.4 to 36%, in contrast to our increase from 10% to 23%. The importance of HPV in opposing the effects of PEEP is illustrated by studies in dogs with experimental left lower lobe pneumonia in which the application of 12 cm H_2O PEEP increased $\dot{Q}l/\dot{Q}t$ from 24 to 37% [28]. These authors found that there was little diversion of blood flow away from lobes with high bacterial counts and attributed the marked shift in blood flow in response to PEEP to a reduction in HPV in the acute stages of the disease.

There have been a number of reports of a reduction in arterial $P\text{O}_2$ in patients subjected to PEEP [2, 3]. This may be caused by an increase in the proportion of blood passing through intrapulmonary shunt pathways, but may also result from a reduction in mixed venous $P\text{O}_2$ secondary to a reduction in cardiac output in the presence of an unchanged $\dot{Q}s/\dot{Q}t$ [29, 30]. However, a number of authors have recorded increases in $\dot{Q}s/\dot{Q}t$ in response to PEEP in patients with predominantly unilateral disease [4–6], and Kanarek and Shannon [7] obtained measurements which confirmed the redistribution of flow to the damaged lung in response to 5 and 15 cm H_2O PEEP in one patient who had been subjected to trauma and who had developed unilateral pneumonia. It is known that trauma to the lung can release prostacyclin which inhibits HPV [31]. HPV is also inhibited by endotoxin [32]. It is thus possible that the shift of blood flow in these patients may have been associated with a poor HPV response.

The adverse response to PEEP seen in patients with predominantly unilateral disease is less obvious in those with diffuse disease [6]. Enjeti and associates [33] have shown that there is a greater reduction in regional blood flow when collapse is restricted to a segment of lung instead of a lobe in closed-chest pigs, and that the application of PEEP does not increase flow to the collapsed segment [34]. On the other hand, Hasan and colleagues [35] found that an increase in $\dot{Q}s/\dot{Q}t$ in acid aspiration injury in dogs occurred at lower PEEP values when the injury was more diffuse than when it was confined to one lung.

The infusion of fluid during lung collapse produced no significant change in $\dot{Q}s/\dot{Q}t$ even though $\dot{Q}t$ was doubled, and PCWP was increased to 19 mm Hg. Benumof and Wahrenbrock [36] found that the vasoconstrictor response to ventilation hypoxia of the left lower lobe in the open chest was halved at this left atrial pressure, whilst in our open-chest experiments $\dot{Q}s/\dot{Q}t$ increased from 0.11 to 0.20 as a result of fluid loading to a left atrial pressure of 21 mm Hg [14]. Since the transmural pressure tending to distend the extra-alveolar pulmonary vessels should have been greater in the collapsed lung in the closed chest than in the lobe in the open chest, this adds further weight to the suggestion that the HPV response was very active in our closed-chest animals. However, the increase in $\dot{Q}t$ resulting from the infusion of fluid was not accompanied by an increase in $P\bar{v}_{O_2}$ or significant reduction in the arterio–venous oxygen content difference in the present experiments. Since there were no large changes in pH or P_{CO_2} which could have affected the position of the oxygen dissociation curve, this suggests that tissue oxygen consumption increased in parallel with the increase in $\dot{Q}t$. The lack of change in $P\bar{v}_{O_2}$ might account for the similarity in the shunt measurements made before and after transfusion, for an increase in $P\bar{v}_{O_2}$ is known to increase flow to a collapsed lobe [37, 38]. The increase in $P_{\overline{PA}}$ and PCWP was similar in our open- and closed-chest experiments, but an increase in flow to the hypoxic lobe was only noted in the open-chest experiments where $P\bar{v}_{O_2}$ increased in parallel with the increase in $\dot{Q}t$. It thus appears that the changes in $P\bar{v}_{O_2}$ may be of more importance in reducing HPV than the change in intravascular pressure when $\dot{Q}t$ is increased by fluid loading.

Although there were no significant increases in $\dot{Q}s/\dot{Q}t$ in response to changes in right mean airway pressure, there was a trend towards an increase in $\dot{Q}s/\dot{Q}t$ with increased pressure in the normovolaemic state. The increase in $P_{\overline{aw}}$ was associated with an increase in Pa_{CO_2} and in arterial-to-end-tidal P_{CO_2} difference, thus suggesting that there was an increase in alveolar deadspace in response to the increase in airway pressure. This provides confirmatory evidence that the increase in airway pressure was having a small effect on flow through the ventilated lung.

It is concluded that the effects of PEEP on the redistribution of blood flow to a collapsed area of lung depend on the relationship between $P_{\overline{aw}}$ and intravascular pressures and on the strength of the HPV response. When the latter is active moderate increases in $P_{\overline{aw}}$ produced by the application of PEEP or changes in the I:E ratio do not increase flow to a collapsed lung in closed-chest dogs.

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EFFECTS OF NITROUS OXIDE ON RESPIRATION DURING HALOTHANE ANAESTHESIA IN THE DOG

L. W. HALL

SUMMARY

The pattern of ventilation was studied in eight greyhounds anaesthetized with halothane in 50% oxygen with nitrogen and in eight with the same concentration of halothane in 50% oxygen with nitrous oxide. There was a significant reduction in both inspiratory and expiratory times in the animals breathing nitrous oxide and an increase in the negative pressures developed in the obstructed airway during inspiration. Measurements during the addition of carbon dioxide to the inspired gases also suggested less respiratory depression in the nitrous oxide breathing group. It was concluded that nitrous oxide may counteract the respiratory depressant effects of halothane.

The administration of nitrous oxide, in concentrations which permit normal oxygenation, does not produce significant anaesthesia or analgesia in dogs and, therefore, it should not be used as the sole anaesthetic agent for surgical manipulations in that species. Also, only minimal advantages are said to be gained when it is used to supplement more potent anaesthetic agents such as halothane [1]. However, in veterinary anaesthesia halothane–nitrous oxide–oxygen mixtures are commonly administered to dogs and there is a widespread clinical impression that this results in spontaneous breathing being better maintained than when halothane is used with oxygen alone. Since 50% nitrous oxide with oxygen has been shown by Steffey and his colleagues [1] to decrease the minimal alveolar concentration (MAC) of halothane for dogs (from 0.87% with oxygen alone to 0.65%) and, since the respiratory depressant effects of this volatile agent are dose-dependent, this supposed greater ventilatory activity is usually attributed to it being possible to maintain anaesthesia with lower concentrations of halothane. However, nitrous oxide has been shown to reduce the respiratory depressant effects of isoflurane in man [2] and, also in man, there is evidence that nitrous oxide alone [3], and mixed with halothane [4], has a mild respiratory stimulant action. It is, therefore, possible that nitrous oxide may counteract the respiratory depression caused by halothane in dogs. The investigation reported here was designed to examine this possibility, using occlusion pressure to assess neural activation of the inspiratory muscles, and the ventilatory response to the inhalation of carbon dioxide as a measure of the sensitivity of the central respiratory control mechanism.

MATERIALS AND METHODS

Experiments were performed in 16 adult greyhounds (11 male) free from clinical evidence of cardiopulmonary disease. No premedication was given and unconsciousness was produced with alfentanil 0.02 mg kg^{-1} i.v. followed immediately by methohexitone 3–4 mg kg^{-1} i.v. Induction of anaesthesia was completed by the administration of halothane volatilized in 50% oxygen with either nitrogen (oxygen-enriched air) or nitrous oxide through a face mask until tracheal intubation with a 12-mm bore, cuffed tracheal tube could be carried out. Anaesthesia was maintained with an inspired concentration of 0.95–1.05% halothane volatilized in the original gas mixture administered through the tracheal tube. A catheter was inserted percutaneously to a femoral artery for measurement of arterial pressure (Kontron System) and sampling for blood-gas determinations (Radiometer ABL3). Body temperature was monitored with a thermistor probe introduced

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through the mouth to the mid-thoracic oesophagus and the animal's body temperature was kept constant to within 0.5 °C by the use of a water blanket. All studies were conducted with the dog lying on its left side and breathing from a T-piece system through a low resistance non-rebreathing valve (Ambu Hesse). A large-bore tap, and a No. 2 Fleisch pneumotachograph head (P. K. Morgan) were placed in the inspiratory limb leading to the Ambu valve. Airway pressure measured from the mouth end of the tracheal tube (Roche Type 800 005 transducer, 1-m fluid-filled line), tidal volume, and inspiratory flow rates, together with the end-tidal carbon dioxide concentration (Medishield MS2 mass spectrometer set to Atomic Mass Unit 44 or, if nitrous oxide was present, linearized Beckman LB1 analyser), were recorded on a four-channel recorder (Lectromed). Inspired concentrations of halothane were measured with an Engstrom medical gas analyser (EMMA) and the pneumotachograph was calibrated with a 1-litre calibrating syringe using the inspired gases for the particular study.

No measurements were made until at least 1 h had elapsed from the time of injection of the methoxhexitone and stable values of inspiratory flow and end-tidal carbon dioxide concentration had been present for at least 30 min. Airway occlusions, each for the duration of a single breath, were imposed after three recorded unobstructed breaths by closing the inspiratory tubing with the large-bore tap during expiration. This was repeated three times, with at least five breaths between observations, to obtain mean values. Following the initial measurements, carbon dioxide was added to the inspired gases to produce an increase in arterial carbon dioxide tension (Pa_{CO_2}) of approximately 2 kPa and a further period of 30 min allowed for stabilization before a second set of measurements was obtained.

The traces were digitized and analysed (Apple IIc microcomputer) to give tidal volume, airway pressure during occlusion and the durations of normal and obstructed inspirations and expirations. The duration of the unobstructed inspiration ($T\mathrm{I}$) was measured from the duration of inspiratory flow. The durations of the occluded inspirations ($T\mathrm{I}^{o}$) were taken as the time from the start of the decrease of airway pressure to the minimum airway pressure during the inspiratory attempt ($P^{\max}$). In addition, measurements were made of the airway pressure 0.1 s after the start of an occluded inspiration ($P^{0.1}$).

Statistical comparison was made with Student's *t* test, or Welch's test when the difference between the variances made the *t* test inappropriate [5].

RESULTS

Eight animals (mean body weight 27.11 kg, SD 5.23) were anaesthetized with halothane in nitrous oxide–oxygen and eight (mean body weight 25.53 kg, SD 3.14) with halothane in nitrogen–oxygen. Mean arterial pressure appeared to be slightly greater in the dogs breathing nitrous oxide (mean 97 mm Hg, SD 15; 94 mm Hg, SD 16, respectively), but the difference was not statistically significant. The heart rates in the two groups were similar at about 120 beat $\min^{-1}$ throughout each experiment. Arterial oxygen tension (Pa_{O_2}) was consistently high throughout each experiment, and in the dogs breathing oxygen enriched air it was not, at the time of the first set of observations, significantly greater than in those breathing nitrous oxide. Also, during the initial period of stable anaesthesia Pa_{CO_2} in the group breathing nitrous oxide, although lower, was not significantly different from that in the other group (mean 6.57 kPa, 95% CI 8.54–6.35; mean 7.45 kPa, 95% CI 7.51–5.62, respectively). Administration of carbon dioxide increased Pa_{CO_2} by a mean of 2.41 kPa in the nitrous oxide group and 1.96 kPa in the other dogs. Tidal volume in the nitrous oxide breathing dogs was slightly greater than in the other group, and the minute volume of ventilation was also greater (table I). In dog No. 13 tidal and minute volumes of ventilation decreased in response to administration of carbon dioxide, while in dog No. A1 tidal volume did not increase when carbon dioxide was added to the inspired gases (fig. 1). However, when calculated on the individual responses obtained, there were significant differences in the tidal volume response ($P = 0.0054$), but not in the minute volume response ($P = 0.101$) to increase in Pa_{CO_2} of 1 kPa.

$T\mathrm{I}$ and ventilatory frequency (f) were significantly shorter in the dogs given nitrous oxide, but inspiration occupied the same fraction of the total ventilatory cycle (T^{tot}) because expiratory time ($T\mathrm{E}$) also decreased and thus the "duty cycle" of the inspiratory muscles was not affected (table I). Since the tidal volumes were similar in the two groups mean inspiratory flow rate ($V\mathrm{T}/T\mathrm{I}$) was greater in the dogs breathing nitrous oxide. In all but one dog in each group, the duration of

TABLE I. *Data from eight dogs (A1–A8) breathing 1% halothane volatilized in a nitrogen–oxygen mixture and eight (1 and 10–16) breathing 1% halothane in nitrous oxide–oxygen. 1 = Values at initial, stable levels of anaesthesia; 2 = values during inhalation of carbon dioxide. * Comparison of the means of the nitrogen and nitrous oxide groups* (t *test*). V_T = *tidal volume*; V = *inspired minute volume*; T_I = *inspiratory time, open airway*; T_I^o = *inspiratory time with airway occluded*; f = *ventilatory rate*; T_I/T^{tot} = *ratio of inspiratory time to total cycle time with unobstructed airway*; V_T/T_I = *mean inspiratory flow rate*

Animal	Pa_{O_2} (kPa)		Pa_{CO_2} (kPa)		V_T (ml kg^{-1})		$\dot{V}$ (ml kg^{-1} min^{-1})		T_I (s)		T_I^o (s)		*f* (b.p.m.)		T_I/T^{tot}		V_T/T_I (ml kg^{-1} s)	
No.	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2
A1	41.60	29.33	6.47	7.67	16	16	168	365	1.00	1.10	1.25	1.50	10.53	16.57	0.175	0.304	16.00	14.55
A2	29.60	21.60	6.00	9.87	8	16	122	351	1.10	0.90	0.80	1.10	15.19	21.43	0.278	0.321	7.27	17.78
A3	35.47	28.67	7.47	11.60	15	19	125	255	1.20	1.10	1.28	1.25	8.36	13.42	0.167	0.246	12.50	17.27
A4	35.60	29.07	5.91	9.60	6	10	54	164	1.28	1.10	1.58	1.70	9.05	16.39	0.227	0.301	5.08	9.09
A5	13.75	18.77	9.20	10.16	14	15	147	252	0.95	0.82	1.17	1.00	10.49	17.14	0.166	0.234	14.74	15.29
A6	20.53	21.07	7.07	7.07	15	18	148	216	1.40	1.30	1.50	1.40	9.84	12.15	0.230	0.263	10.71	13.85
A7	29.87	22.13	8.53	11.07	9	11	125	239	0.80	0.70	0.90	0.80	13.86	21.74	0.185	0.254	11.25	15.71
A8	36.00	22.67	8.93	11.87	16	24	133	279	1.37	1.34	1.57	1.51	8.33	11.60	0.190	0.259	11.68	17.96
Mean	30.30	24.16	7.45	9.86	12.4	16.1	128	265	1.14	1.05	1.26	1.28	10.71	16.31	0.202	0.273	11.15	15.56
SD	9.15	4.19	1.31	1.74	4.0	4.5	33	67	0.21	0.22	0.29	0.30	2.53	3.86	0.039	0.032	3.60	3.086
1	37.87	41.47	4.93	8.27	17	29	347	417	0.65	1.00	1.42	1.42	20.41	14.55	0.221	0.242	26.15	21.07
10	38.80	37.07	7.33	8.93	11	14	102	336	0.69	0.74	1.01	1.14	9.24	23.48	0.106	0.289	15.94	18.72
11	37.07	38.27	6.67	10.00	9	23	154	432	0.67	0.74	1.27	1.15	17.14	18.83	0.191	0.232	13.43	31.08
12	27.73	38.67	7.73	8.93	8	17	92	436	0.74	0.70	0.87	0.99	11.56	25.53	0.143	0.298	10.81	17.17
13	39.07	40.00	7.07	7.87	16	13	264	228	0.45	0.72	0.70	0.85	16.53	17.78	0.124	0.219	35.56	15.29
14	36.16	36.53	5.47	7.07	8	14	141	418	0.98	0.75	0.70	0.85	17.60	28.92	0.287	0.361	8.16	18.67
15	36.27	32.13	5.47	7.33	12	28	189	611	0.57	0.84	0.74	1.11	15.75	22.06	0.150	0.309	21.05	33.33
16	34.67	33.73	7.87	8.53	25	28	315	351	0.75	0.80	1.08	1.08	12.63	12.55	0.158	0.167	33.33	35.00
Mean	35.96	32.73	6.57	8.37	13.3	20.8	201	404	0.69	0.79	0.97	1.07	15.11	20.46	0.171	0.265	20.55	23.79
SD	3.63	11.97	1.13	0.95	5.9	7.0	97	109	0.15	0.10	0.27	0.19	3.67	5.56	0.060	0.061	10.29	1.98
**P*	0.14	0.088	0.173	0.052	0.74	0.138	0.075	0.008	0.0002	0.013	0.066	0.11	0.014	0.105	0.24	0.75	0.037	0.022

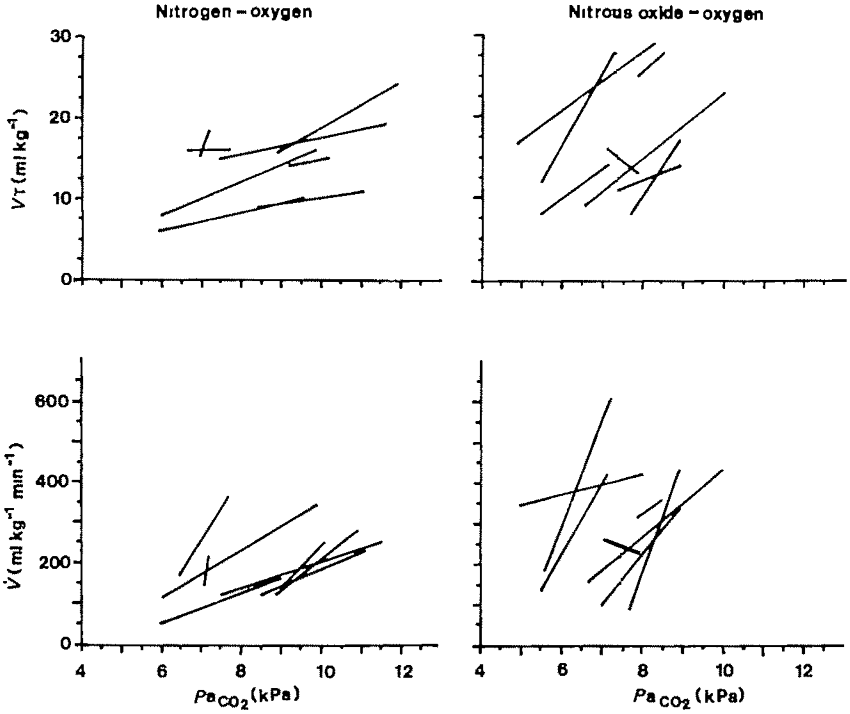

FIG. 1. Ventilatory responses to inhalation of carbon dioxide in eight dogs anaesthetized with halothane in nitrogen–oxygen and in eight anaesthetized with halothane in nitrous oxide–oxygen, showing the generally steeper response in those breathing nitrous oxide.

inspiration with the airway obstructed ($T\text{I}^{\text{o}}$), was longer that $T\text{I}$; the mean increase with nitrous oxide was 0.37 (SD 0.26) s and in the other group 0.18 (SD 0.09) s (fig. 1). Under similar conditions of Pa_{CO_2}, expiratory time after an occluded inspiration ($T\text{E}^{\text{o}}$) was not significantly different from that after an unobstructed inspiration ($T\text{E}$) in each of the two groups.

The maximum sub-atmospheric pressure ($P^{\max}$) developed in the occluded airway was significantly greater in the nitrous oxide group (table II), and the airway pressure 0.1 s ($P^{0.1}$) after the beginning of an obstructed inspiration was also significantly greater in this group, as was the rate of decrease in pressure ($P^{\max}/T\text{I}^{\text{o}}$).

Administration of carbon dioxide produced inconsistent changes in $T\text{I}$. In seven of the eight dogs in the first group, and in two of the eight breathing nitrous oxide, $T\text{I}$ was shortened, but in six of those breathing nitrous oxide $T\text{I}$ was prolonged. $T\text{I}^{\text{o}}$ showed a slight increase with increase in Pa_{CO_2}; the principal effect of adding carbon dioxide to the respired gases in both groups was a decrease in $T\text{E}$, with an increase in $T\text{I}/T^{\text{tot}}$, but only in the nitrogen group was the reduction in $T\text{E}$ significant ($P = 0.003$).

$P^{\max}$ and $P^{0.1}$ were both markedly increased by the inhalation of carbon dioxide, as was the rate of change in pressure during obstruction of the airway, $P^{\max}/T\text{I}^{\text{o}}$.

Plotting the logarithms of the values of the subatmospheric airway pressure during an obstructed inspiration, measured at 0.1-s intervals for the first 0.5 s of the inspiratory attempt, against the logarithms of time, showed that the relationship between them was linear; the regression lines are shown in figure 2. The correlation coefficients were highly significant, ranging from 0.9992 to 0.9518 and the patterns of change in airway pressure (as expressed by the means of the intercepts and slopes (table III)) did not differ significantly between the two groups of animals at the initial values of Pa_{CO_2}.

DISCUSSION

In these studies the concentration of halothane was not reduced when nitrous oxide was admin-

TABLE II. *Data from nitrogen breathing and nitrous oxide breathing dogs during halothane anaesthesia. 1 = Values at initial, stable levels of anaesthesia; 2 = values during inhalation of carbon dioxide.* $T_I{}^o - T_I$ *= difference between duration of inspiration during obstructed and unobstructed breathing.* P^{max} *and* $P^{0\,1}$ *= maximum subatmospheric pressure developed in the obstructed airway during inspiration and the pressure developed 0.1 s after the commencement of inspiration against obstruction.* $P^{max}/T_I{}^o$ *= rate of development of the subatmospheric pressure. Effective impedance =* $(P^{max}/T_I{}^o)/(V_T/T_I)$

	$T_I{}^o - T_I$ (s)		$P^{0.1}$ (cm H_2O)		P^{max} (cm H_2O)		$P^{max}/T_I{}^o$ (cm H_2O s^{-1})		Effective impedence	
Dog No.	1	2	1	2	1	2	1	2	1	2
A1	0.25	0.40	1.82	3.64	24.54	39.40	19.63	26.27	1.365	2.160
A2	−0.30	0.20	1.82	3.64	16.40	27.30	20.50	24.82	2.820	1.763
A3	0.80	0.15	0.99	1.14	12.20	19.35	9.53	15.48	0.860	1.107
A4	0.30	0.60	0.73	1.03	16.57	28.89	10.49	16.99	2.571	1.408
A5	0.22	0.18	0.87	3.91	20.59	26.87	17.60	25.87	1.304	1.653
A6	0.10	0.10	1.36	1.37	16.38	21.39	11.22	15.28	0.971	1.112
A7	0.10	0.10	1.36	4.55	15.91	20.50	17.68	25.63	1.717	1.818
A8	0.20	0.17	0.96	0.91	20.25	34.30	12.90	22.72	0.796	1.346
Mean	0.12	0.24	1.23	2.52	17.86	27.25	14.94	21.76	1.551	1.546
SD	0.19	0.17	0.43	1.54	3.77	6.995	4.38	5.013	0.771	0.368
1	0.77	0.42	1.76	4.40	22.45	29.92	15.81	21.15	0.786	1.211
10	0.32	0.27	1.29	4.60	24.40	42.20	24.16	37.02	1.684	1.635
11	0.60	0.41	2.64	9.09	20.02	68.05	15.76	59.33	1.760	2.411
12	0.13	0.29	1.76	5.87	34.00	31.39	39.48	31.80	1.014	2.270
13	0.25	0.13	3.99	8.55	32.49	49.02	46.41	57.67	1.815	4.317
14	−0.28	0.10	2.20	6.16	16.43	28.12	23.47	33.16	3.269	2.584
15	0.17	0.27	5.75	8.80	26.69	45.76	36.07	41.23	2.200	1.619
16	0.33	0.00	3.76	6.58	36.66	28.83	33.94	26.39	1.200	1.275
Mean	0.29	0.24	2.89	6.76	26.64	40.54	29.39	38.47	1.716	2.165
SD	0.32	0.15	1.50	1.86	7.17	13.78	11.27	13.79	0.782	1.011
P	0.22	0.99	0.016	0.0002	0.008	0.029	0.007	0.006	0.677	0.14

istered and thus, if MAC values of inhalation anaesthetics are additive, the depth of central nervous depression should have been greater in the group of dogs which received nitrous oxide than in the group which did not [6–9]. In spite of this, even though in these studies not all the measured differences reached statistical significance, the results tend to suggest better respiratory function in the dogs breathing halothane with nitrous oxide after induction with alfentanil and methohexitone. They support the possibility that nitrous oxide protects against halothane-induced respiratory depression by producing central stimulation and the view of Steffey and colleagues [1]—that only minimal advantages are to be gained when nitrous oxide is administered with halothane—must be questioned. It would seem that the inclusion of nitrous oxide in the gases inspired by the spontaneously breathing dog could be beneficial and, while the widely held impression that its use during halothane anaesthesia decreases respiratory depression by allowing lower halothane concentrations to be used could well be sound, it may not be necessary to reduce the halothane concentration for benefit to be obtained.

Central respiratory drive was assessed by measurement of the decrease in pressure in the obstructed airway during inspiration since in the anaesthetized animal this pressure is proportional to measurements of neural output to the ventilatory muscles [10, 11], provided certain factors remain unchanged. For example, any change in the initial length of the muscle of the diaphragm or of the intercostal muscles would affect muscular efficiency and could invalidate a comparison of occlusion pressures for different postures or at a different functional residual capacity (FRC). In this investigation all the dogs were lying on their left sides and FRC may have been influenced by the inhalation of nitrous oxide or carbon dioxide, although these effects are likely to be small. Chest wall rigidity must also be taken into account when comparing measurements of occlusion pressure,

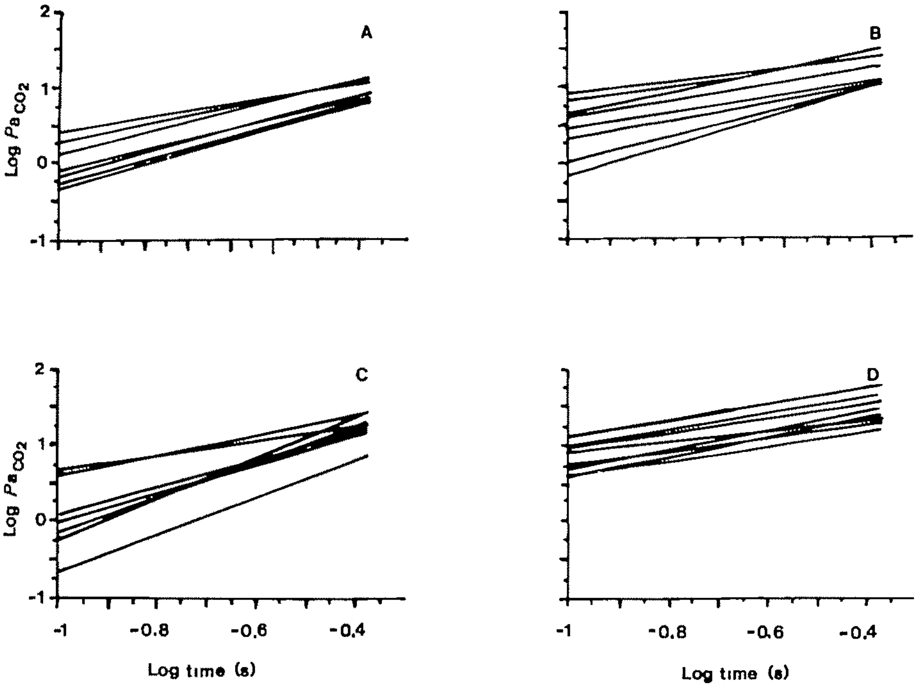

FIG. 2. Regression lines for plots of log $P^{0\,1}$ against log time at 0.1-s intervals for the first 0.5 s of an inspiration with the airway occluded. Intercepts and slopes are given in table III. A: Eight dogs during initial stable anaesthesia with halothane in oxygen-enriched air; C: same dogs during inhalation of carbon dioxide; B: second group of eight dogs during initial stable anaesthesia with halothane in nitrous oxide–oxygen; D: second group during inhalation of carbon dioxide.

or inspiratory flow rates ($V\text{T}/T\text{I}$), since the greater $P^{\max}$ and $P^{\max}/T\text{I}^0$ ratio in the nitrous oxide group could be taken to suggest that the chest wall may have been stiffer in these animals. Reflexes at a spinal level, related to intercostal muscle activity, might increase chest wall rigidity [12], but other published evidence suggests that opioid–nitrous oxide combinations increase muscle rigidity by supraspinal effects rather than by increased excitability of spinal motor neurones [13]. The possibility that supraspinal activity induced by an interaction between alfentanil and nitrous oxide more than 1 h after the administration of alfentanil 0.02 mg kg^{-1} may have produced this effect cannot be excluded since, although Arndt, Bednarski and Parasher [14] found the half-life of alfentanil for respiratory effects in conscious dogs to be 15–25 min, the evidence from the present studies relating to the timing of events in the ventilatory cycle suggests a longer period of action. It might be postulated that differences in chest wall stiffness would be apparent from the airway pressure trace because a more compliant chest wall could move inwards as the diaphragm moves back, reducing the pressure generated by the diaphragm. This could account for the pressure waveforms recorded by Marsh, Rehder and Hyatt [15] during occluded inspirations in dogs under enflurane anaesthesia where the development of airway pressure was delayed. However, in the present study there was no indication of any delay in the generation of the sub-atmospheric airway pressure during occluded inspirations in either of the two groups of dogs. In the apparent absence of any evidence of major differences in chest wall stiffness, the finding that the mean values of $P^{\max}$ and $P^{\max}/T\text{I}^0$ were significantly greater ($P < 0.05$) in the nitrous oxide group can probably be taken to indicate a greater central ventilatory drive in these dogs. In addition, $T\text{I}$ was significantly shorter in the nitrous oxide group, indicating that the significantly greater $P^{\max}$ in these animals cannot simply reflect a primary difference in $T\text{I}$. Moreover, the increase in $P^{\max}$ and $P^{\max}/T\text{I}^0$ with increase in Pa_{CO_2} should still indicate the ability of the

TABLE III. *Intercepts and slopes of the regression lines plotted in figure 2.* r^2 = *coefficient of determination and* r = *coefficient of correlation. 1 = Data relevant to initial stable level of anaesthesia; 2 = data relevant to period of inhalation of carbon dioxide*

	Intercept		Slope		r^2		r	
Dog No.	1	2	1	2	1	2	1	2
A1	1.5054	1.5673	1.2801	0.9354	0.9730	0.9842	0.9864	0.9921
A2	1.4370	1.7351	1.0808	1.1261	0.9883	0.9562	0.9941	0.9778
A3	1.4279	1.6687	1.7894	1.5850	0.9688	0.9565	0.9843	0.9780
A4	1.5080	1.4543	1.7621	2.0937	0.9698	0.9757	0.9848	0.9878
A5	1.6636	1.5786	1.5770	0.8553	0.9685	0.9476	0.9841	0.9735
A6	1.4532	1.6596	1.7484	1.6839	0.9852	0.9321	0.9925	0.9655
A7	1.6044	2.0620	1.3988	2.2257	0.9059	0.9109	0.9518	0.9544
A8	1.1613	1.7861	1.1005	1.9235	0.9297	0.9984	0.9642	0.9992
Mean	1.5255	1.6815	1.4626	1.5536				
SD	0.0885	0.1891	0.2891	0.5279				
1	1.6041	1.6621	0.9960	0.7465	0.9863	0.9988	0.9931	0.9994
10	1.6581	2.0390	1.7977	1.4291	0.9914	0.9062	0.9957	0.9520
11	1.3906	2.0204	0.9526	1.0239	0.9958	0.9637	0.9979	0.9817
12	1.5411	1.6606	1.5411	0.9096	0.9852	0.9846	0.9926	0.9923
13	1.9275	1.8792	1.2690	0.9167	0.9841	0.9945	0.9920	0.9973
14	1.7930	2.1462	0.9872	1.0252	0.9926	0.9848	0.9963	0.9924
15	1.6161	1.8995	0.7556	1.1161	0.9903	0.9595	0.9951	0.9795
16	1.3866	1.6006	1.0666	0.9958	0.9956	0.9791	0.9978	0.9895
Mean	1.6146	1.8635	1.1707	1.0204				
SD	0.1849	0.2027	0.345	0.1982				

bulbopontine centres, coupled with the available power of the ventilatory muscles, to produce adequate tidal and minute volumes of ventilation with different anaesthetic agents. From the mean values, in both groups of dogs an increase of approximately 30 % of the original Pa_{CO_2} produced a 50 % increase in P^{max} and a 30–40 % increase in P^{max}/T_I^{o}, showing evidence of ample available gain in the system.

In addition, the effective impedance $(P^{max}/T_I^{o})/(V_T/T_I)$, where P^{max} and V_T are measured at similar times, should indicate the mechanical behaviour of the ventilatory system, since occlusion pressure should remain an index of the force potentially available for inspiration, and there were no significant differences between the effective impedances. However, the strongest evidence for increased respiratory centre output in the dogs breathing nitrous oxide was the increased $P^{0.1}$ which is unaffected by ventilatory system resistance and compliance or by vagal volume-related activity [16].

The increase in Pa_{CO_2} of about 2 pKa was chosen to keep the response below the value at which the dog's response begins to decline and to where the response is approximately linear [17]. However, results in two of the dogs indicate that the higher values of Pa_{CO_2} attained may have been starting to be depressant. Arterial oxygen tension was always high so the slope and position of the lines should not have been influenced by hypoxaemia and, if the response in dogs is similar to that in man [18, 19], their slope and position might be taken to reflect the depth of anaesthesia. With increasing depth of anaesthesia the carbon dioxide responses move progressively to the right and the slope of the relation is depressed progressively. Thus the fact that the response to the carbon dioxide challenge in the dogs breathing nitrous oxide is to the left and steeper than in the other group might seem to indicate that breathing nitrous oxide resulted in a decrease in the depth of anaesthesia. However, these results might equally well demonstrate a more localized effect of nitrous oxide in the brain, since the most important site of the chemoreceptor response to carbon dioxide lies in the neurones near the ventral surface of the medulla, which react to a reduction of pH of brain extracellular fluid; nitrous oxide may merely enhance this response, rather than produce a decrease in anaesthetic depth as a result of a more generalized effect in the brain as a whole. In this context, it is of interest that stimulation of specific regions of the brain could be invoked to explain the very high MAC of nitrous oxide in dogs.

The finding that V_T was slightly increased by nitrous oxide does not agree with that of Hornbein and co-workers [4] in man, in whom the addition of nitrous oxide to a constant halothane concentration produced a decrease in V_T which was offset by an increase in the rate of ventilation. However, even in these dogs an increase in rate was the major effect, as can be seen from the greater minute volumes recorded. Although there is, on average, a lower Pa_{CO_2} and a higher Pa_{O_2} in the nitrous oxide breathing group during undisturbed spontaneous ventilation they do not match the greater total ventilation, presumably as a result of a greater proportion of deadspace ventilation. The pattern of breathing under nitrous oxide–oxygen–halothane is different to that under nitrogen–oxygen–halothane but, from these experiments, there is no clear evidence that alveolar ventilation is greater relative to metabolic rate. It is possible, however, that the addition of nitrous oxide during halothane anaesthesia increases the metabolic rate because there is evidence that it increases sympathetic activity [4].

In all but one dog in each of the groups T_I^o exceeded T_I, showing that in 14 of the 16 dogs termination of inspiration was influenced by vagal activity (Hering–Breuer reflex). There was some indication that nitrous oxide enhanced this influence because the mean increase in inspiratory time during airway occlusion in the animals breathing this gas was about 54% compared with 15% in the other dogs. This activity of the Hering–Breuer reflex in dogs is also suggested by the results of Marsh, Rehder and Hyatt [15], who investigated the effects of halothane and enflurane. They found a significant prolongation of T_I during occluded inspiration during enflurane anaesthesia, and a smaller increase, which was not statistically significant, under halothane anaesthesia. The values recorded for T_I were shorter and the Pa_{CO_2} values were lower than those found in the present study in spite of apparently greater depths of anaesthesia. In a related study [20] it was found that there was little change in ventilatory timing with depth of halothane anaesthesia so the longer T_E and smaller $T_I : T^{tot}$ ratios in the study presented here suggest that the alfentanil given at induction may, in spite of its apparently favourable pharmacokinetics, have had an influence on ventilatory timing and, possibly, central ventilatory drive. However, its effects on ventilatory timing should have been similar in the two groups of dogs and should not, therefore, have influenced the differences in the ventilatory patterns found in this study.

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INFLUENCE OF PRETREATMENT WITH A MONOAMINE OXIDASE INHIBITOR (PHENELZINE) ON THE EFFECTS OF BUPRENORPHINE AND PETHIDINE IN THE CONSCIOUS RABBIT

J. E. MACKENZIE AND L. W. FRANK

SUMMARY

The existence of a severe toxic interaction (occasionally fatal) from the clinical use of pethidine and monoamine oxidase (MAO) inhibitors is well established. The present study evaluates the possibility of such an interaction existing for the opioid partial agonist buprenorphine. Conscious rabbits ($n = 6$ *in each group) pretreated 18–24 h previously with physiological saline or the MAO inhibitor phenelzine 20 mg kg*$^{-1}$ *s.c. were subsequently given physiological saline, pethidine 5 mg kg*$^{-1}$ *i.v. or buprenorphine 0.1 or 1.0 mg kg*$^{-1}$ *i.v. Whilst saline was without effect and phenelzine produced only a small increase in the rabbit temperature, the combination of phenelzine and pethidine produced a marked, prolonged hyperpyrexia* ($+4.4 \pm 0.19$ °C; $P < 0.001$), *hypertension* ($+33.9 \pm 3.1$ mm Hg; $P < 0.01$) *and agitation. Three rabbits died, at 35, 45 and 55 min after the pethidine–phenelzine combination. Buprenorphine was without significant effect on any parameter when given after phenelzine. In the model used buprenorphine, in contrast to pethidine, showed no interaction with the MAO inhibitor phenelzine.*

A severe toxic interaction occurs when patients, treated with monoamine oxidase (MAO) inhibitors, are given the narcotic analgesic pethidine [1–4]. The symptoms exhibited by these patients include cyanosis, profuse sweating and Cheyne–Stokes ventilation. Patients become semiconscious, may pass into coma and have died [2].

Although there has not been any report of such an interaction between buprenorphine and MAO inhibitors, it is important that the possibility of such an interaction be investigated.

It is possible to demonstrate the MAO inhibitor–pethidine interaction in mice [5, 6], rats [7] and rabbits [7, 8]. The rabbit was chosen as the subject of this study as the interaction is particularly marked (especially on body temperature). In addition, arterial pressure and heart rate are readily monitored in the conscious rabbit.

Previous studies of this interaction have used a range of doses of phenelzine varying from 10 h pretreatment with 5 mg kg^{-1} [7] to 50 mg kg^{-1} at 42 and 18 h before administration of pethidine [8]. The dose of pethidine most commonly used is 5 mg kg^{-1}. In the present study, preliminary investigations using a range of doses and pretreatment times with phenelzine showed that a strong interaction with pethidine 5 mg kg^{-1} i.v. occurred after pretreatment with phenelzine 20 mg kg^{-1} s.c., given 18–24 h previously. The doses of buprenorphine were chosen from analgesic data in the conscious rabbit, where 0.1 mg kg^{-1} i.v. was a threshold dose, the ED_{50} was 0.2 mg kg^{-1} and maximum analgesia was produced with 1.6 mg kg^{-1} i.v. [9]. As buprenorphine exhibits a "bell-shaped" dose–response curve, producing less effect with higher doses, a low dose (0.1 mg kg^{-1}) and a high, but submaximal, analgesic dose (1.0 mg kg^{-1}) were chosen.

MATERIALS AND METHODS

Male, New Zealand white rabbits in the weight range 1.8–2.75 kg were treated with either

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physiological saline 1 ml kg^{-1} s.c. or phenelzine 20 mg kg^{-1} s.c. 18–24 h before study. On the day of the investigation the rabbits were lightly anaesthetized with halothane to allow the placement of a rectal thermometer probe (Bailey Instruments, Type RET-1); the resulting body temperature was displayed on a digital temperature display (Bailey Instruments, Model BAT 8). Whilst the animal was anaesthetized, a 23-gauge Mediwing infusion set was inserted to an ear vein to allow administration of the test compounds. Similarly, a 23-gauge needle, connected to a Hewlett–Packard 1280C pressure transducer via a length of polypropylene tubing (pp 50), filled with heparinized saline 20 units ml^{-1}, was inserted to an ear artery for the recording of arterial pressure via a Hewlett–Packard 8805C carrier amplifier. The recording of arterial pressure was used to calculate heart rate. The animals were allowed to recover from the anaesthesia before the start of the definitive investigation. Body temperature, arterial pressure and heart rate were monitored every 10 min for up to 30 min before the administration of test drugs, to ensure the stability of all variables. The animals then received pethidine 5 mg kg^{-1} i.v., buprenorphine 0.1 or 1.0 mg kg^{-1} i.v. or physiological saline 1 ml kg^{-1} i.v. Variables were monitored every 5 min for up to 60 min following the administration of the test compound.

Drugs

Buprenorphine (Reckitt and Colman); pethidine (Macfarlan–Smith); phenelzine SO_4 (Sigma). Drugs were dissolved and diluted in 0.9% sodium chloride (Boots, Steriflex). The dose volume for all drugs was 1 ml kg^{-1}.

Data analysis

The mean effect at each measurement was calculated and the standard error of the mean

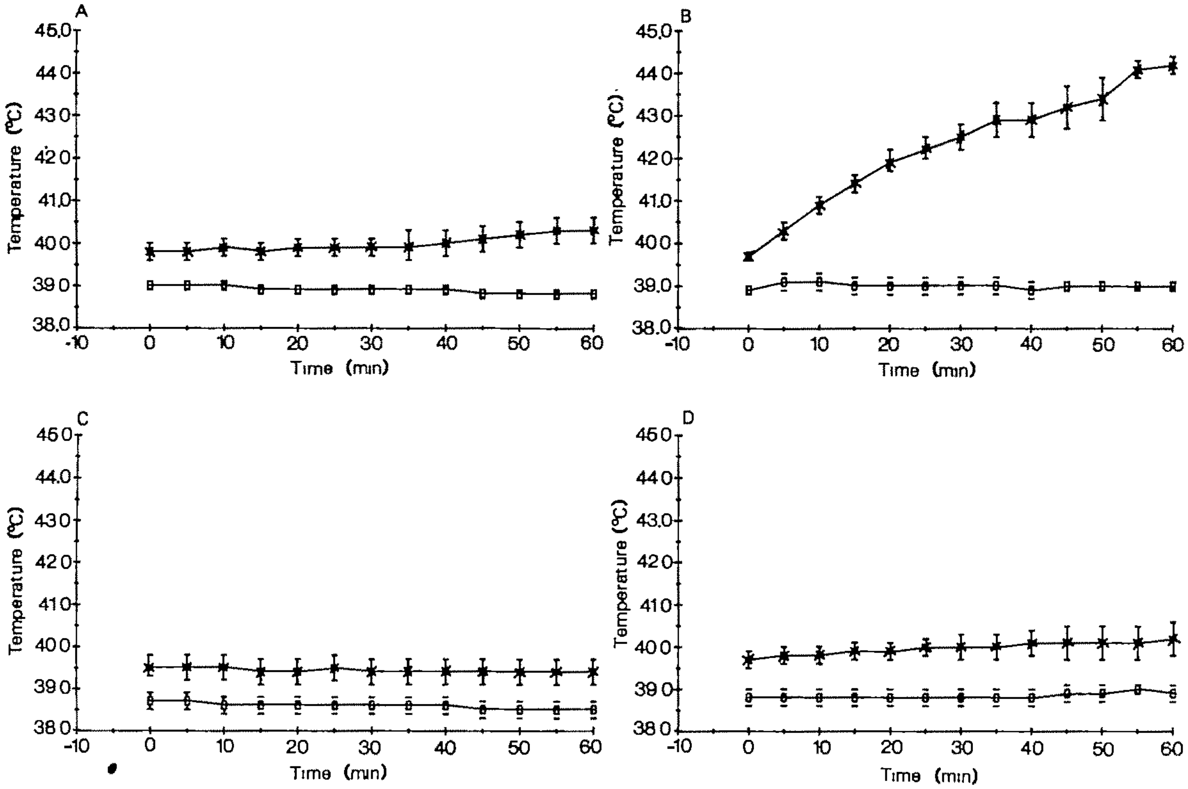

FIG. 1. The influence of physiological saline 1 ml kg^{-1} i.v. (A), pethidine 5 mg kg^{-1} i.v. (B), buprenorphine 0.1 mg kg^{-1} i.v. (C) or buprenorphine 1.0 mg kg^{-1} i.v. (D) on the temperature of the conscious rabbit after pretreatment 18–24 h previously with either saline 1 ml kg^{-1} s.c. (□) or phenelzine 20 mg kg^{-1} s.c. (x). Each point represents the mean of six observations.

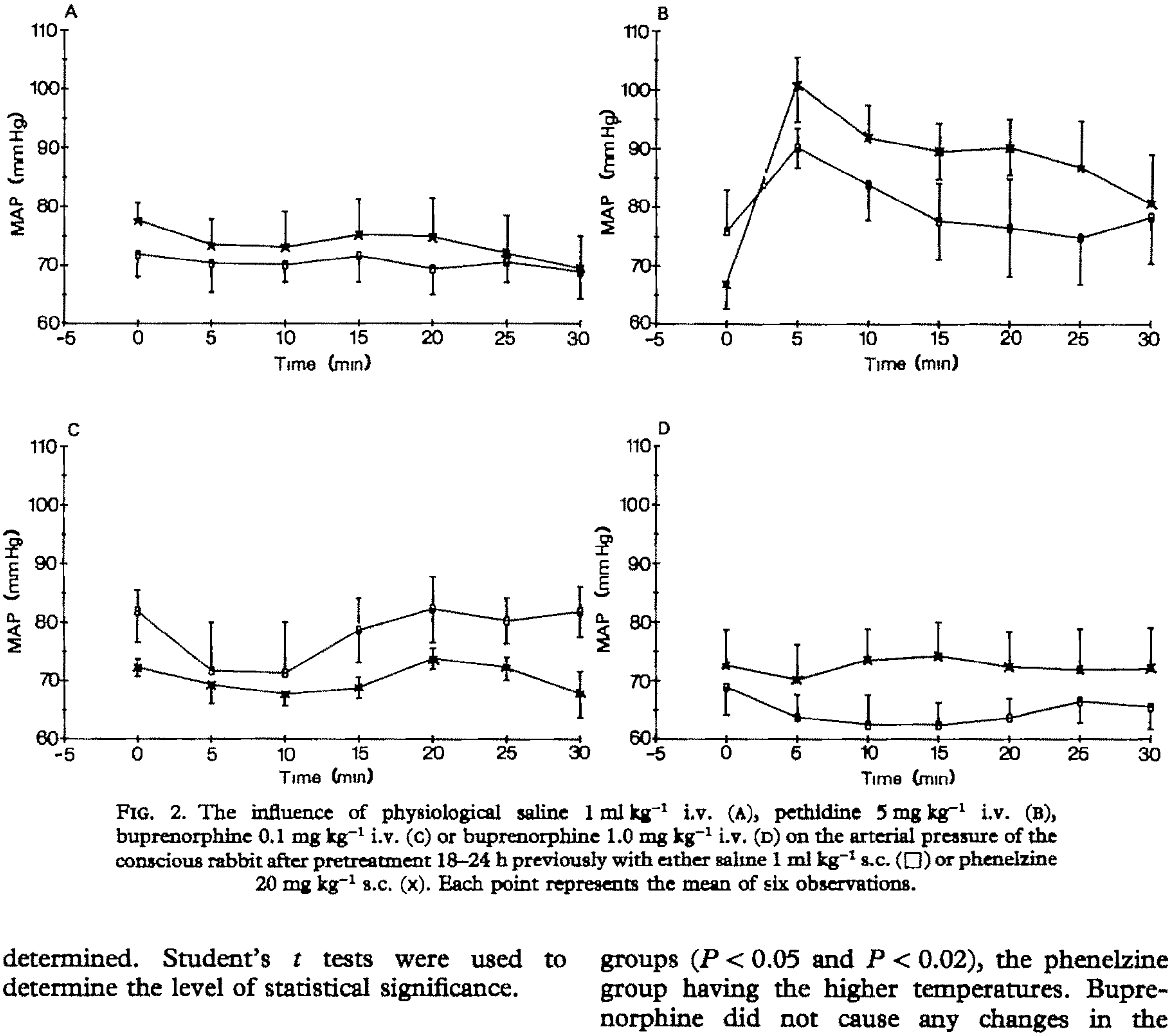

FIG. 2. The influence of physiological saline 1 ml kg^{-1} i.v. (A), pethidine 5 mg kg^{-1} i.v. (B), buprenorphine 0.1 mg kg^{-1} i.v. (C) or buprenorphine 1.0 mg kg^{-1} i.v. (D) on the arterial pressure of the conscious rabbit after pretreatment 18–24 h previously with either saline 1 ml kg^{-1} s.c. (□) or phenelzine 20 mg kg^{-1} s.c. (x). Each point represents the mean of six observations.

determined. Student's *t* tests were used to determine the level of statistical significance.

RESULTS

Body temperature

Saline. Rabbits pretreated 18–24 h previously with physiological saline 1 ml kg^{-1} s.c. or phenelzine 20 mg kg^{-1} s.c. showed no change in body temperature when subsequently given saline 1 ml kg^{-1} i.v. (fig. 1A). However, those rabbits pretreated with phenelzine had significantly higher pre-challenge temperatures ($P < 0.02$) than the saline-pretreated group.

Buprenorphine. Buprenorphine 0.1 mg kg^{-1} or 1.0 mg kg^{-1} i.v., when given to rabbits pretreated with either phenelzine or saline, was without effect on body temperature (fig. 1C, D). However, there was a significant difference in temperature between the phenelzine- and saline-pretreated groups ($P < 0.05$ and $P < 0.02$), the phenelzine group having the higher temperatures. Buprenorphine did not cause any changes in the behaviour of the animals in either the saline- or phenelzine-treated animals.

Pethidine. Pethidine 5 mg kg^{-1} i.v. caused a large increase in body temperature ($+4.4 \pm 0.19$ °C; $P < 0.001$) in those animals which had been pretreated with phenelzine. The increase in body temperature was rapid in onset and was statistically significant ($P < 0.01$) from 5 min after the administration of the pethidine, and continued to increase for the duration of the investigation (fig. 1B). The combination of pethidine and phenelzine produced gross changes in animal behaviour: the rabbits exhibited symptoms of hyperexcitement, tremor and increased motor restlessness, including nodding and jumping. Three rabbits died after the combination of phenelzine and pethidine (35, 45 and 55 min after the pethidine).

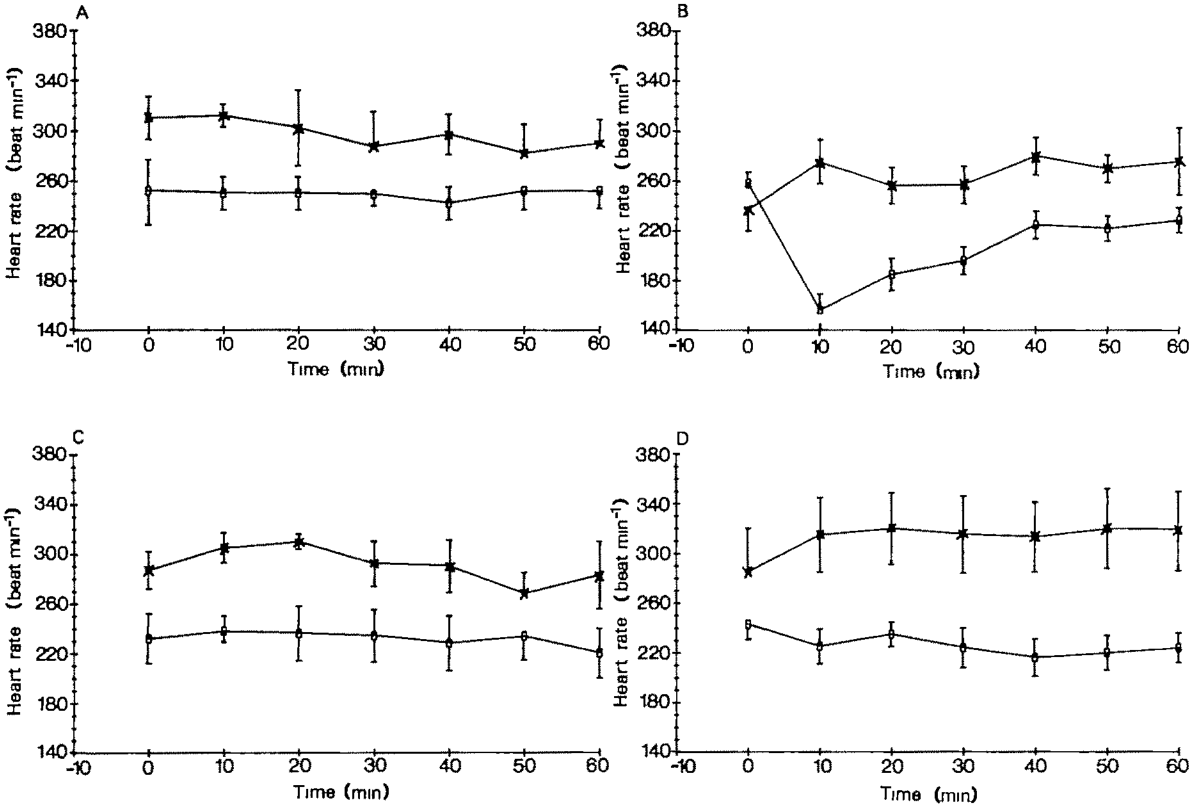

FIG. 3. The influence of physiological saline 1 ml kg^{-1} i.v. (A), pethidine 5 mg kg^{-1} (B), buprenorphine 0.1 mg kg^{-1} i.v. (C) or buprenorphine 1.0 mg kg^{-1} i.v. (D) on the heart rate of the conscious rabbit after pretreatment 18–24 h previously with either saline 1 ml kg^{-1} s.c. (□) or phenelzine 20 mg kg^{-1} s.c. (x). Each point represents the mean of six observations.

In saline-pretreated rabbits, pethidine did not produce an alteration in body temperature (fig. 1B), nor did the animals show any changes in behaviour. As with the other test groups, phenelzine-pretreated animals had significantly higher starting temperatures ($P < 0.01$) than the saline-pretreated group.

Arterial pressure and heart rate

Saline. When given to rabbits pretreated with either physiological saline or phenelzine, there were small non-significant decreases in mean arterial pressure (fig. 2A) and heart rate (fig. 3A).

Buprenorphine. In animals pretreated with saline, the lower dose of buprenorphine 0.1 mg kg^{-1} i.v. was associated with a small, but not significant decrease (-9.4 ± 5.7 mm Hg), in arterial pressure (fig. 2C). There was no change in heart rate (fig. 3C). The higher dose of buprenorphine (1.0 mg kg^{-1} i.v.) was without effect on arterial pressure (fig. 2D); there was a small (-26.7 ± 12.0 beat min^{-1}) although not-significant decrease in heart rate (fig. 3D).

Buprenorphine 0.1 and 1.0 mg kg^{-1} i.v. given to rabbits 18–24 h after phenelzine pretreatment was without effect on arterial pressure (fig. 2C, D) and produced only small, and not-significant, changes in heart rate (fig. 3C, D).

Pethidine. In saline-pretreated rabbits the administration of pethidine 5 mg kg^{-1} i.v. resulted in a small, but non-significant increase in arterial pressure. After pretreatment with phenelzine, pethidine produced an increase in mean arterial pressure (fig. 2B). The change in arterial pressure produced by pethidine seen in the phenelzine-treated group ($+33.9 \pm 3.1$ mm Hg) was significantly different ($P < 0.05$) from the change in arterial pressure produced in the saline-pretreated group ($+14.3 \pm 6.8$ mm Hg). However, the increase in arterial pressure with the pethidine–phenelzine combination was highly significant relative to both pre-pethidine controls and the saline control group ($P < 0.001$). Whilst pethidine, in saline-pretreated animals, resulted in a significant ($P < 0.001$) decrease in heart rate (-102.5 ± 12.0 beat min^{-1}), in phenelzine-treated animals it produced a progressive tachycardia (maximum change $+42.5 \pm 21.7$ beat min^{-1}) (fig. 3B).

DISCUSSION

It was clear from the present investigation that the interaction between pethidine and phenelzine is very severe, confirming the studies by Jounela [7] and Loveless and Maxwell [8]. The interaction was much more severe than the 1–1.5 °C increase that would result as a response to a bacterial pyrogen. Bacterial pyrogen responses were not evident in the present study, with no changes in temperature after i.v. administration in the saline group. The increase in temperature after the combination of phenelzine and pethidine was of rapid onset and developed throughout the whole period of observation. This was in contrast to the effects on arterial pressure, which peaked within 5 min of the injection of pethidine.

The observation that pethidine alone produced a small pressor response and marked bradycardia also confirmed the results of Jounela [7], who attributed these effects of pethidine to an indirect release of catecholamines. The lack of bradycardia after phenelzine pretreatment may be the result of further enhancement of catecholamine concentrations such that direct cardiac stimulation opposed the reflex bradycardia. It is not clear by what mechanism the pethidine–phenelzine interaction occurs, although it has been shown that inhibition of both A and B types of MAO are required for pethidine to produce the effect [10]. Although there are a number of publications implicating increased concentrations of 5-hydroxytryptamine (5-HT), the effect is not only related to 5-HT concentrations but may, in addition, be caused by increased concentrations of dopamine or noradrenaline, or both [11], which may account for the differing time courses of the changes in cardiovascular indices and in temperature. The effect of the MAO inhibitor agent is not simply the result of a reduction in metabolism, as complete inhibition of the liver microsomal enzymes which metabolize pethidine does not induce the toxic effects noted [10]. Whatever the cause of the pethidine–MAO inhibitor interaction, it is clear from the present studies that buprenorphine does not interact with the MAO inhibitor phenelzine. Morphine is similarly without toxic sequelae when administered in conjunction with a MAO inhibitor [7, 12–15]. Penn and Rogers [14] also showed that the opioid pentazocine did not produce a toxic interaction with the MAO inhibitor pargyline. In addition, there are no reports of clinical observations of a toxic interaction between MAO inhibitors and opioids other than pethidine. Thus, it would appear that MAO inhibitors have a very specific interaction with pethidine, and that a general interaction with opioids does not exist.

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MONOAMINE OXIDASE INHIBITORS AND ANAESTHESIA

A Review

C. G. STACK, P. ROGERS AND S. P. K. LINTER

SUMMARY

There has been a recent renewal of interest in the use of monoamine oxidase inhibitors in psychiatry. The concurrent administration of anaesthetic agents, particularly narcotic analgesics, is often a cause for concern. Although many monoamine oxidase inhibitor–drug interactions have been reported, in practice it is only the interaction with pethidine which has led to fatalities. What is not appreciated is that the monoamine oxidase inhibitor–pethidine interaction has two distinct forms—"excitatory" and "depressive". It is this lack of appreciation that has led to much confusion when dealing with patients taking monoamine oxidase inhibitors.

Iproniazid was synthesized in the early 1950s and used in the treatment of tuberculosis. Its antituberculous properties failed to meet expectations, but clinicians noted evidence of central stimulation [34]. Research into this observation attributed the central effects of iproniazid to the inhibition of monoamine oxidase (MAO). There has been recent renewal of interest in the use of monoamine oxidase inhibitors (MAOI) [14], since other forms of treatment for depression and phobias are still far from satisfactory, especially in those patients who appear to respond to treatment with MAOI. During the past three decades, there have been numerous reports of MAOI–drug interactions, often serious or fatal. Some of these relate to routine anaesthetic practice.

ACTIONS OF MAO

Two MAO subtypes have been identified [37]: type A preferentially deaminates noradrenaline and 5-hydroxytryptamine (5-HT), whilst type B deaminates phenylethylamine.

Monoamine oxidase is one of the two main enzymes involved in the inactivation of non-methylated biogenic amines (the other is catechol-o-methyl transferase (COMT)) (fig. 1). Within the adrenergic neurone, noradrenaline is stored in a stable pool (combined with adenosine triphosphate (ATP)), and in a mobile pool ready for immediate release (fig. 2). There is a constant turnover of the stable pool and MAO is the mediator. It acts to limit the size of the stored pool. Inhibition of MAO leads to a larger stable pool and, hence, a greater mobile pool.

MAO is also found in other types of neurone within the brain which use dopamine or 5-HT as transmitters. Here it serves essentially the same function. In other parts of the body, MAO is found principally in the liver and gut, where its function is to metabolize potentially hazardous amines.

MAOI act by forming a stable, irreversible complex with MAO; the main target seems to be cerebral neuronal MAO. Therefore, the size of the amine pools is no longer limited and, as a result, the amount of noradrenaline available for release in the neurone, increases. However, these effects are not confined to the brain and the concentration of noradrenaline also increases within the sympathetic nervous system. Since the majority of MAOI cause irreversible enzyme inhibition, their effects are prolonged, because the synthesis of new enzyme is a slow process.

MAOI INTERACTIONS WITH ANAESTHETIC AGENTS

Narcotic analgesics

Narcotic analgesics play an essential part in anaesthetic practice. Strong analgesics are often

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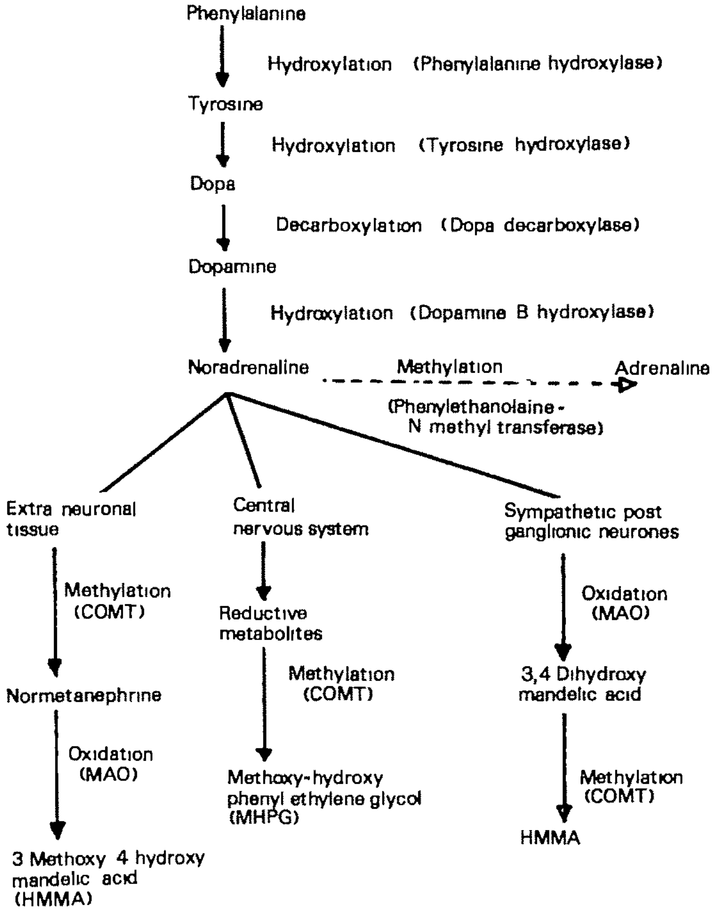
Phenylalanine
Hydroxylation (Phenylalanine hydroxylase)
Tyrosine
Hydroxylation (Tyrosine hydroxylase)
Dopa
Decarboxylation (Dopa decarboxylase)
Dopamine
Hydroxylation (Dopamine B hydroxylase)
Noradrenaline
Methylation
Adrenaline
(Phenylethanolaine - N methyl transferase)
Extra neuronal tissue
Central nervous system
Sympathetic post ganglionic neurones
Methylation (COMT)
Reductive metabolites
Oxidation (MAO)
Methylation (COMT)
3,4 Dihydroxy mandelic acid
Normetanephrine
Oxidation (MAO)
Methoxy-hydroxy phenyl ethylene glycol (MHPG)
Methylation (COMT)
HMMA
3 Methoxy 4 hydroxy mandelic acid (HMMA)

FIG. 1. Synthesis and catabolism of noradrenaline. COMT = Catechol-o-methyl transferase; MAO = monoamine oxidase.

required for the relief of severe pain or as part of the anaesthetic regimen during surgery. When patients taking MAOI present in these situations, there is concern about a potentially fatal interaction on the one hand, and the inadequate relief of pain on the other. What is not appreciated is that the MAOI–narcotic interaction has two distinct forms:

First, an "excitatory" form (type 1) characterized by sudden agitation, unmanageable behaviour, headache, hyper- or hypo-tension, rigidity, hyperpyrexia, convulsions and coma. It is thought to be attributable to central serotonergic overactivity.

Second, a "depressive" form (type II) consisting of respiratory depression, hypotension and coma, as a result of the inhibition of hepatic microsomal enzymes by the MAOI, leading to accumulation of free narcotic. Pethidine is the only commonly used narcotic to have elicited the excitatory response, which is, however, frequently severe and often fatal.

Pethidine. The first reported interaction between pethidine and MAOI concerned a 60-yr-old doctor treated for pulmonary tuberculosis with iproniazid [22]. He developed severe muscle twitching, profuse perspiration, hyperreflexia and upgoing plantar responses within 20 min of receiving pethidine 100 mg i.m. He recovered. Iproniazid also had a vogue in the treatment of intractable angina and three cases were reported of similar, sudden deterioration after the additional administration of pethidine [24, 33]. Further reports appeared of seven psychiatric patients receiving a variety of MAOI who were given pethidine for surgery, labour pains, severe headache or backache [9, 10, 12, 23, 28, 38]. Six had a sudden excitatory reaction; two of them

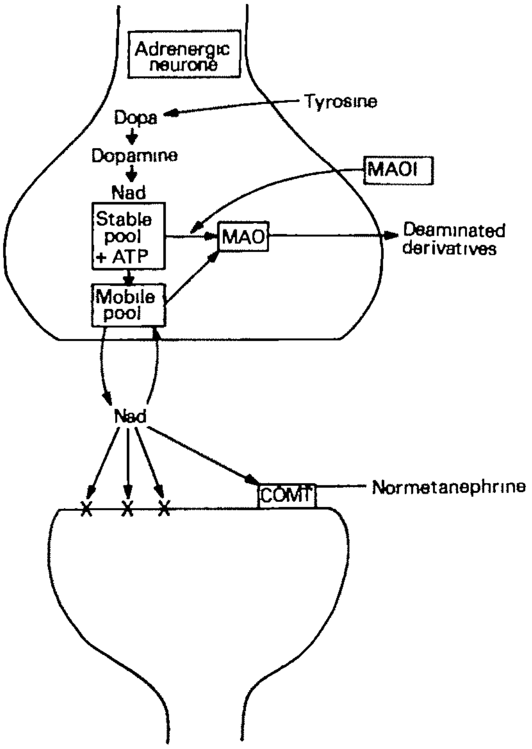

FIG. 2. Representation of the adrenergic neurone and the site of activity of the monoamine oxidase inhibitors, to increase the stable and mobile pools of noradrenaline. COMT = Catechol-o-methyl transferase; MAO = monoamine oxidase; MAOI = monoamine oxidase inhibitor; Nad = noradrenaline.

died. Further cases of pethidine–MAOI interactions continue to be reported, and an animal study is presented in this issue [18].

Based on studies in animals, it has been postulated that the excitatory response is caused by an increase in the cerebral 5-HT concentration. This follows the inhibition of monoamine oxidase [30] and is potentiated by pethidine, which blocks the neuronal uptake of 5-HT [7]. This reaction occurs in about 20% of cases, probably because it is necessary to exceed a critical cerebral 5-HT concentration to trigger the response [27]. Animals pre-treated with inhibitors of 5-HT synthesis do not exhibit an increase in cerebral 5-HT concentration, or the excitatory response. However, other authors have suggested that this may be an idiosyncratic reaction [13].

Should an excitatory response occur, hypertension is treated ideally with an alpha-adrenoreceptor blocking agent, such as phentolamine or with peripheral vasodilators, such as hydrallazine or sodium nitroprusside. If these are not available, parenteral chlorpromazine [7, 24] is useful as an anti-hypertensive, antipyretic and general sedative. Hydrocortisone [12] or prednisolone [33] may also be useful. Cardiac arrhythmias may be treated with beta-adrenergic blocking drugs. Acidification of the urine will increase the rate of clearance of pethidine to a small degree [17].

Morphine. In a comprehensive review of MAOI interactions, Stockley [36] wrote that "the serious pethidine–MAOI interaction also cast a shadow over morphine, resulting in the appearance of morphine in a number of lists and charts of drugs that were said to interact with the MAOI". However, another review [1] concluded that "no documentation supports the involvement of narcotic analgesics other than pethidine with the MAOIs". Two patients [23, 33] who had severe excitatory reactions to pethidine (one fatal) had previously been given morphine with no adverse effects. Brown and Waldron [6] safely gave morphine 20 mg i.m. to five patients who developed severe headache and retrosternal discomfort whilst receiving tranylcypromine.

Sargant [32] knew "of some ten cases with no side effects except a more prolonged morphine action". Thus, morphine has been recommended as the narcotic analgesic of choice in the presence of MAOI administration [1]. Morphine does not block neuronal 5-HT uptake, but its narcotic effects may be potentiated in the presence of MAOI. A single case report of a type II (depressive) reaction following morphine has been described [29]. The patient, who was receiving tranylcypromine, was given a pre-operative trial of incremental morphine i.v. After the third dose (a total of 6 mg of morphine) she became hypotensive and unconscious. Naloxone 0.4 mg i.v. restored arterial pressure to normal and the patient to full consciousness. This case illustrated the importance of careful titration of i.v. morphine against clinical response in a patient taking MAOI, when pain relief is required in an emergency. Should a depressive reaction occur, treatment is mainly supportive. Noradrenaline is the most reliable vasopressor. Indirectly-acting sympathomimetic agents (such as metaraminol) that have mixed actions also release endogenous noradrenaline and so risk provoking a hypertensive overshoot—as a result of the increase in noradrenaline concentration in the sympathetic nerve endings. Naloxone, as in the above case report, or hydrocortisone [12] may be useful.

Respiratory depression may require assisted ventilation.

Other narcotics. Dextromethorphan (Cosylan), like pethidine, blocks neuronal 5-HT uptake. Rivers and Horner [29] reported a fatal interaction. A 26-yr-old woman receiving phenelzine 15 mg 6-hourly for depression consumed 60 ml of a cough mixture containing dextromethorphan. Within 1 h she became unconscious, rigid and severely hypotensive with fixed dilated pupils. Core temperature was 42 °C. She died despite attempted resuscitation.

Phenoperidine is probably best avoided as its main metabolites are norpethidine and (to a lesser extent) pethidine. Papaveretum is a mixture of morphine and other opiate alkaloids and would appear to have no advantage over morphine. Pentazocine has been studied in animals, in which interactions with MAOI have occurred [31], but it is not clear if this occurs in man. Methadone has been given concurrently with tranylcypromine, both at 30 mg daily for 3 months without mishap, in a drug addict who developed depression while on a withdrawal programme [20]. There is anecdotal evidence to support the safety of fentanyl in the presence of MAOI. There is no information about alfentanil or meptazinol. For buprenorphine, see the paper by Mackenzie and Frank in this issue [18].

Induction agents

Studies in animals suggest that MAOI may have a non-specific inhibitory effect on hepatic microsomal enzymes. Because of this, potentiation of barbiturates may be expected. This has been found in animals [39], although there is a case report of hypotension following induction with sodium thiopentone [16]. The patient had received morphine and hyoscine as premedication. The same authors give anecdotal evidence of prolongation of the effect of thiopentone by MAOI.

Although no interactions have been reported with the use of ketamine and MAOI, theoretically, it should be avoided in patients taking MAOI because of the stimulatory response of the cardiovascular emergence phenomenon after ketamine.

Neuromuscular blocking agents

Phenelzine has been shown to decrease pseudocholinesterase concentration; accordingly, there have been case reports of a prolonged effect from suxamethonium [3, 5]. This may lead to apnoea following suxamethonium and may modify the fit during electroconvulsive therapy.

There is no information regarding interactions with non-depolarizing neuromuscular blocking drugs. However, since pancuronium bromide releases stored adrenaline, it is a theoretical hazard.

Vecuronium, atracurium or alcuronium would all appear to be suitable alternatives.

Anti-emetics

Phenothiazines. Although the combination of MAOI and phenothiazines has been recommended in patients with psychiatric conditions, three reputed fatalities have been reported with this combination [2, 19]. However, none of these cases involved the use of a phenothiazine as an anti-emetic. In fact, chlorpromazine is considered a good sedative for treatment of the hypertensive excitatory reaction induced by MAOI.

Droperidol. There is solitary report of hypotension in a patient taking MAOI, who was given a relatively large dose (20 mg) of droperidol as premedication, 4 days after ceasing his psychiatric medication [26]. There is no evidence that this was an interaction.

Anticholinergics

There is no confirmed interaction between anticholinergic drugs and MAOI. Hyperthermia has been reported in animals and, theoretically, atropine would worsen any excitatory interaction of MAOI. Sheehan, Claycomb and Kouretas [34] stated that "anticholinergics are significantly potentiated" by MAOI.

Anaesthetic gases and volatile agents

Nitrous oxide, halothane, enflurane and isoflurane are all safe in the presence of MAOI. There is a report that rats, pre-treated with MAOI, required a greater minimum alveolar concentration of cyclopropane for anaesthesia [21].

These drugs also have inhibitory actions on other enzyme systems, most notably the hydroxylation and oxidation systems in liver microsomes [35]. Therefore, theoretically, there is a chance of increased reductive metabolites of halothane being formed. Thus, although no reports of any problems exist, there is an increased possibility that halothane could cause hepatic damage.

Local anaesthetic preparations

The only known report of an interaction between a local anaesthetic drug and an MAOI was with cocaine, which was used in a patient also given pethidine and local adrenaline [9]. It has been recommended that adrenaline-containing solutions should be avoided. If a vasoconstrictor is thought to be necessary, felypressin is a suitable alternative.

Regional blockade can be utilized for postoperative analgesia.

Other associated agents used during anaesthesia

Doxapram. Based on animal studies, it has been suggested that pretreatment with MAOI potentiates the therapeutic and side effects of doxapram [36]. The manufacturers recommend caution with its use, although there are no clinical data available.

Benzodiazepines. The concurrent use of MAOI and benzodiazepines is usually considered safe. There have been, however, two reports of gross oedema which was attributed to a benzodiazepine–MAOI interaction [15, 25].

Sympathomimetic agents. Agents such as amphetamine, ephedrine and metaraminol act partially by releasing endogenous noradrenaline and adrenaline and risk provoking a fatal hypertensive crisis. During treatment with MAOI, large amounts of noradrenaline accumulate, not only in the brain, but also within sympathetic nerve endings in general. *Indirectly-acting sympathomimetics* will release these stores and produce an exaggeration of the normal physiological response. This is a serious and possible lethal interaction [36]. Hypertensive reactions can be treated with alpha-adrenoceptor blocking agents (such as phentolamine) or directly-acting vasodilators (such as sodium nitroprusside or nitrates) [7]. Chlorpromazine i.m. can also be used.

Directly-acting sympathomimetic agents (noradrenaline, adrenaline, isoprenaline) are the surest and most reliable pressor agents in the presence of MAOI. However, care must be taken, since it appears that their effects may be enhanced by receptor hypersensitivity. This augmentation of effect is unlikely to be clinically hazardous, except in those patients who show a marked hypotensive response to MAOI [4, 11]. These patients may show a several-fold enhancement of the pressor effects of noradrenaline.

DISCUSSION

Anaesthesia for patients taking MAOI has been a cause of concern to anaesthetists for many years. Advice that MAOI should be stopped 10–14 days before anaesthesia is unreasonable on two counts. First, MAOI are often a treatment of last resort: they are commonly used to good effect in patients who have been unresponsive to other forms of therapy; to discontinue effective treatment and compromise the patient's psychiatric status is, we believe, unreasonable. Second, MAOI form a stable complex with MAO and thus further MAO has to be synthesized; this is a long process. Adverse reactions to narcotic analgesics, have been noted even 3 weeks after discontinuing therapy.

As is seen in the history of MAOI–drug interactions, it is only with pethidine (and dextromethorphan) that the fatal excitatory reaction is seen. Reference is often made to the test dose procedure of Churchill-Davidson [8]. This involves giving small incremental doses of pethidine over a period of several hours in an attempt to demonstrate sensitivity to pethidine. This is hardly appropriate in the emergency situation where adequate analgesia is required immediately. More importantly, pethidine is the only narcotic analgesic used in anaesthesia to have elicited fatal excitatory interactions.

It would seem unnecessary to persist with pethidine in this test dose procedure, when the safety of morphine has been established.

CONCLUSION

Patients taking monoamine oxidase inhibitors should continue to do so before elective surgery. Per- and postoperative pain relief using regional blockade is a safe alternative to general anaesthesia.

If necessary, for emergency or elective surgery, morphine (in reduced dosage) is the narcotic analgesic of choice. Pethidine must never be administered to patients receiving MAOI.

When general anaesthesia is required there is a wide range of suitable anaesthetic agents. However, the dangers of sympathetic overactivity must be remembered.

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MUSCLE RELAXATION IN PATIENTS WITH DUCHENNE'S MUSCULAR DYSTROPHY

Use of Vecuronium in Two Patients

W. BUZELLO AND H. HUTTARSCH

SUMMARY

Cumulative 50% and 90% neuromuscular blocking doses of vecuronium were determined in two 4-yr-old boys with Duchenne's muscular dystrophy. Vecuronium 20 $\mu g\ kg^{-1}$ was required for 50% twitch depression in both patients. The 90% blocking doses were 43 and 57 $\mu g\ kg^{-1}$. Although these data do not indicate a greater than normal sensitivity to vecuronium, the recovery time (75–25% block) of twitch tension was three to almost six times as long as in normal children. The evoked compound EMG, additionally recorded in one patient, reflected almost the same dose–response relationship as twitch tension, yet the EMG recovered faster than the twitch. The present findings do not exclude an increased sensitivity to neuromuscular blocking drugs in a larger population of patients with muscular dystrophy. Thus, the titration of the individual neuromuscular blocking dose with the aid of a nerve stimulator is mandatory. During a previous anaesthetic, cardiac arrest and acute rhabdomyolysis had occurred in one patient. The substitution of suxamethonium by vecuronium, or probably any other non-depolarizing myoneural blocking drug of intermediate or short duration of action, may help to avoid this complication.

Duchenne's muscular dystrophy, an inherited X-linked disease, is characterized by severe muscle weakness which is the result of a progressive decrease in the total number of muscle fibres. The disease presents in early childhood, and affects particularly the muscles of the pelvic girdle and thigh [1,2]. Its significance in the management of general anaesthesia has been reviewed in previous articles [3,4]. However, a search of the literature failed to reveal any specific recommendations as to the choice, or dose, of non-depolarizing neuromuscular blocking agents based on evoked twitch recording or on electromyography (EMG). We describe two patients, with particular reference to neuromuscular monitoring and the potential hazards of the use of myoneural blocking drugs in patients with muscular dystrophy.

CASE REPORTS

Patient 1

The significant features of the history of this 4-yr-old boy (98 cm, 16 kg) were motor retardation with inability to lift his head, to crawl, or to achieve a sitting position at the age of 9 months. The diagnosis of Duchenne's muscular dystrophy was established at that time, based on a marked increase in plasma creatine phosphokinase concentration (4640 u. litre^{-1}), and on muscle biopsy. No halothane contracture test was performed. Hospital admission on the present occasion was for the repair of bilateral inguinal herniae. Premedication consisted of fluopromazine 5 mg and pethidine 10 mg i.m., 45 min before the induction of anaesthesia. Anaesthesia was induced with halothane and nitrous oxide in oxygen, administered by face mask. Orotracheal intubation was performed without the aid of a neuromuscular blocking drug. Anaesthesia was maintained with 67% nitrous oxide and halothane (1–1.5 vol% inspiratory concentration) in oxygen administered through a non-rebreathing system. Neuromuscular transmission was monitored by

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TABLE I. *Neuromuscular transmission in two patients with Duchenne's muscular dystrophy following incremental i.v. administration of vecuronium. ED_{50} and ED_{90} = cumulative 50% and 90% blocking doses [5], respectively, determined from depression of twitch tension and amplitudes of the evoked compound electromyogram (EMG). *Extrapolated: 64–37% block = 12 min*

	ED_{50} (µg kg^{-1})	ED_{90} (µg kg^{-1})	Recovery time (75–25% block) (min)
Patient 1			
Twitch	20	43	22*
EMG	19	37	14
Patient 2			
Twitch	20	57	40

the simultaneous recording of the evoked twitch tension of the left adductor pollicis muscle and the evoked compound EMG of the left thenar eminence in response to supramaximal train-of-four stimulation of the ulnar nerve at the wrist every 15 s. Three 10-µg kg^{-1} doses of vecuronium, injected i.v. 30 min after the induction of anaesthesia at 3-min intervals, resulted in a 70% and 78% depression of twitch tension and EMG amplitudes (measured from peak to peak), respectively. Neuromuscular transmission was then allowed to recover spontaneously. The boy did well during anaesthesia and surgery, and the trachea was extubated uneventfully 7 min after completion of the 40-min procedure. Almost equal dose–response relationships were calculated from the EMG and twitch tracings, whereas *recovery time* was 8 min shorter when assessed by the EMG than when determined using the twitch tension (table I).

Patient 2

This boy had been anaesthetized repeatedly for closed reduction of bilateral club foot. No complications were reported, when he was 1 yr of age, during the first three anaesthetics which were with halothane and nitrous oxide in oxygen, administered via an anaesthetic face mask or tracheal tube. The fourth procedure was complicated by cardiac arrest with acute rhabdomyolysis, immediately following the i.v. administration of suxamethonium 10 mg. Cardiopulmonary resuscitation was successful; however, the child suffered persisting brain damage. This incident prompted further investigation which, on the basis of an increase in creatine phosphokinase concentration (5918 u. litre^{-1}), neurophysiological examination and muscle biopsy, led to the diagnosis of Duchenne's muscular dystrophy. In addition, the result of an *in vitro* halothane contracture test (1 vol%) was consistent with susceptibility to malignant hyperthermia. A right-sided amaurosis and convergent strabismus were noted 1 year after the incident. Two years later (the present occasion) the child (now 4 yr, 99 cm, 19 kg) was anaesthetized for a further attempt to correct his club foot deformity. Premedication was with morphine 4 mg and pentobarbitone 60 mg injected i.m. 1 h before the induction of anaesthesia, which was with thiopentone 100 mg i.v., 67% nitrous oxide in oxygen via face mask with assisted ventilation, and fentanyl 0.10 mg i.v. in divided doses. Neuromuscular transmission was monitored by means of evoked twitch tension as described above. After stabilization of the recording system, vecuronium was injected i.v. in 12 2.5-µg kg^{-1} doses over 25 min. The resulting 83% twitch depression provided satisfactory conditions for tracheal intubation. Neuromuscular transmission was then allowed to recover spontaneously. Anaesthesia was uneventful, and nasopharyngeal temperature remained constant at 36.8 °C. The tracheal tube was removed 20 min after the completion of surgery. The data on neuromuscular transmission are shown in table I, where the 40-min *recovery time* is particularly remarkable.

DISCUSSION

In normal children, Goudsouzian and colleagues [6] found the cumulative 90% blocking dose of vecuronium to be 51 ± 16 µg kg^{-1} (mean ± SD). The corresponding figures in the present patients were within these limits, indicating that these two patients did not have a greater than normal sensitivity to vecuronium. However, these data do not permit statistical analysis or interpatient comparison, nor do they generally exclude an increased sensitivity of patients with muscular dystrophy to non-depolarizing myoneural blocking drugs. Increased sensitivity to non-depolarizing blockers might be expected, particularly in the advanced stages of the disease. We would, therefore, recommend the individual titration of the dose of neuromuscular blocker with the aid of a nerve stimulator, even though the adductor pollicis muscle may not be fully accurate in predicting the contractile force of the ventilatory muscles in the presence of muscle disease [7, 8].

Duchenne's muscular dystrophy confers a risk of delayed postoperative ventilatory failure which has occurred as long as 36 h after uneventful general anaesthesia [4]. Therefore, particular care should be taken to ensure complete restoration of muscle contractility before ventilatory support is discontinued. Despite normal sensitivity to vecuronium, the present patients showed a three- to almost six-fold prolongation of the *recovery time* (75–25 % block) (normal children: 9 ± 1.6 min [6]). In myasthenia gravis, the evoked twitch tension has been found to be more sensitive in reflecting the delayed recovery of neuromuscular transmission than the EMG action potentials [8]. The data of patient 1 suggest that this applies also to Duchenne's muscular dystrophy.

The history of patient 2 should serve as a further warning as to the susceptibility of patients with muscular dystrophy to severe cardiac arrhythmia or cardiac arrest. Acute rhabdomyolysis has been observed to occur in connection with cardiac complications [9–11]. The scarcity of well documented cases does not allow a definite conclusion as to whether acute rhabdomyolysis with cardiac arrest should be regarded as a variant of malignant hyperthermia or as a syndrome in its own right [3, 12]. A triggering effect of suxamethonium is generally accepted [4]; however, the role of halothane remains to be defined. Richards [3] reported 37 uneventful halothane anaesthetics in patients with Duchenne's muscular dystrophy. Subsequent authors published three cases of rhabdomyolysis and cardiac arrest after halothane anaesthesia without the use of suxamethonium [9, 11]. Yet, one author questioned the significance of halothane while focusing attention on pre- or postoperative hypoxaemia which may have gone unnoticed [9]. Likewise, a recent textbook does not mention halothane as being contraindicated in Duchenne's muscular dystrophy [13]. Also, no adverse effects of halothane were noticed in patient 1, whereas cardiac arrest had previously occurred in patient 2 when, apart from halothane, suxamethonium was also involved.

Both the risk of delayed postoperative ventilatory failure unrelated to muscle paralysis [4] and the slow recovery from vecuronium-induced neuromuscular blockade should preclude the use of long-acting neuromuscular blocking drugs such as tubocurarine, pancuronium and alcuronium. In addition, pharmacological antagonism of persisting non-depolarizing neuromuscular blockade should not be attempted. It may be anticipated that, like suxamethonium, the accumulation of acetylcholine at the motor end-plate secondary to the administration of anticholinesterase agents may trigger rhabdomyolysis. Adverse neuromuscular reactions to neostigmine in dystrophia myotonica and progressive muscle dystrophy have been reported previously [14].

With reference to the management of anaesthesia in patients with Duchenne's muscular dystrophy, it can be concluded: (i) Vecuronium, and probably any non-depolarizing neuromuscular blocker of intermediate or short duration of action, may be used safely if, with the aid of a peripheral nerve stimulator, the dose is assessed on an individual basis. (ii) The duration of neuromuscular blockade may be prolonged although the patient's sensitivity to vecuronium, and probably any other non-depolarizing neuromuscular blocker, may be normal. (iii) The evoked compound EMG may be less reliable in reflecting the recovery of neuromuscular transmission than the evoked twitch tension.

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THE HALOSCALE "INFANTA" WRIGHT RESPIROMETER

An In Vitro *and* In Vivo *Assessment*

D. J. HATCH AND G. M. E. WILLIAMS

SUMMARY

The performance of the Haloscale "Infanta" respirometer has been assessed in vitro *using ISO test compliances and resistances, and* in vivo *by comparison with pneumotachograph volumes in 13 spontaneously breathing children and 13 children during intermittent positive pressure ventilation. The Infanta was shown to be capable of registering volumes between 15 and 200 ml with an accuracy of ±5%. The registered volume decreased rapidly below 15 ml, whilst above 200 ml over-registration developed.*

The Wright respirometer [1] has been used for many years for the measurement of tidal and minute volumes in adults and children of 20 kg body weight and over. As with any turbine instrument, performance decreases markedly at low gas flow rates. The recently-introduced Infanta turbine contains modifications designed to increase the sensitivity of the instrument so as to produce a simple device for measuring volume in infants and children, and in any patient with severe ventilatory weakness.

The purpose of this study was to assess the performance of this device *in vitro* and *in vivo*, and to verify its working range.

MATERIALS AND METHODS

The Infanta modifications

The Infanta instrument (Ferraris Medical Ltd) was designed primarily for the measurement of ventilation in infants with tidal volumes of as little as 15 ml, and not for measuring continuous gas flows. Increased sensitivity was achieved in four ways. First (fig. 1), a barrier was placed across the outer gallery of the turbine (1) so that the flow of gas cannot divide and stagnate on the side opposite the point of entry. Second, the slots in the stator (2) through which gas passes to reach the rotor vane were reduced in length compared with the adult instrument, and graduated so that each slot gives an equal impulse to the vane. Third, the deadspace of the instrument was decreased to 14 ml by filling much of the gallery around the exterior of the stator (3). The principle of the barrier was proposed by Professor S. P. Hutton, who with Dr J. A. Bushman and one of the authors (G.W.) contributed the graduation of the slots and reduction of deadspace. The dividing of the dial was also altered (by G.W.) so that it effectively increases the reading sensitivity whilst conveniently retaining the same gear ratio used in the standard instrument. Calibration jets were chosen which cause a percentage of the flow to bypass the slots in the stator and enable accurate calibration, as in the standard model, but a finer degree of adjustment is required to achieve the stated performance.

Resistance is 0.24 kPa litre^{-1} s at 15 litre min^{-1}.

Methods of testing: in vitro

Volume studies. The apparatus used to determine the volume calibration of the Infanta respirometer (fig. 2) was a modification of the ventilator performance recording system described by Newton, Hillman and Varley [2] using the same ISO test compliances (a) and resistances (b), kindly loaned by Dr Newton, to simulate infant pulmonary conditions. The smallest Starling pump (stroke volume 0–200 ml) was used instead of the Nuffield ventilator and Newton value. The volume between the pump and the test lung was 54 ml.

The volume registration of the Infanta was

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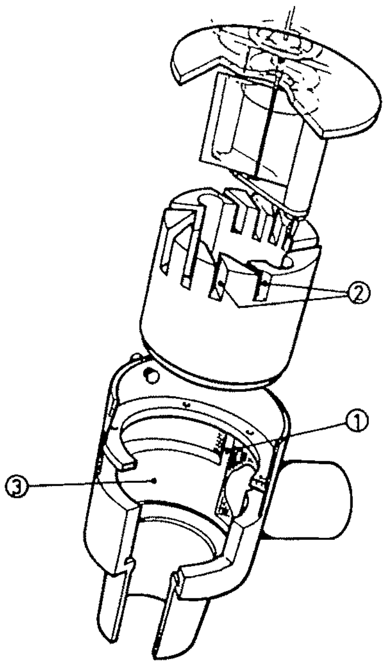

FIG 1. Exploded view of Haloscale "Infanta" respirometer. 1 = Barrier across outer gallery of turbine; 2 = stator slots; 3 = decreased deadspace of gallery.

calibrated against the volume swept per stroke by the Starling pump piston. To verify that there were no leaks in the system, the output of the Starling pump was compared with the geometrically integrated volume from the flow signal of a Mercury Electronics pneumotachograph type F100L (c) connected to a Mercury Electronics differential pressure transducer type M7 (d). The output from this transducer was recorded on a Kipp and Zonen chart recorder type BD8 (e). The pneumotachograph was assessed for linearity, and calibrated over the range 0–100 litre min^{-1} in each direction using automatically timed constant flows passed into a dry gas meter which had been calibrated previously at 16 and 60 litre min^{-1} by reference to an absolute gas holder (Parkinson and Cowan No. 1112).

Volume measurements were obtained by measurement of the area between the flow signal and zero flow line. Simultaneous tidal volume measurements were obtained from the Infanta respirometer and the pneumotachograph using the mean volume of 10 successive pump strokes. Frequency was varied stepwise between 25 and 60 min^{-1}, for tidal volumes between 15 and 200 ml.

Flow studies. When the instrument had been calibrated by reference to known simulated tidal volumes, the respirometer was subjected to a range of continuous flows from 1 to 20 litre min^{-1}. At 1 and 2 litre min^{-1} the volume registered was compared with flow passed through an accurate flowmeter (Rotameter Mfg. Co: Serial No. 817481/61; range 0.3–3 litre min^{-1}. With flows greater than 2 litre min^{-1}, the comparison was with the volume passed through the dry gas meter described above, while time was measured electronically.

Methods of testing: in vivo.

Simultaneous measurements of tidal volume were obtained from the Infanta respirometer and a pneumotachograph placed in series in the breathing system in infants and young children

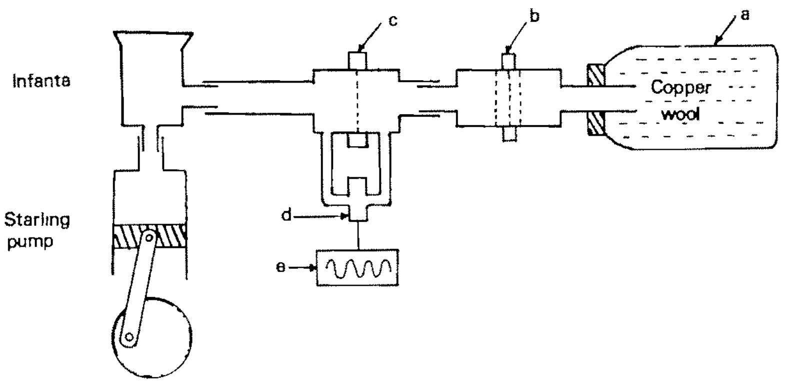

FIG. 2. Test lung system used for *in vitro* studies. Compliances of 10, 30, 100 and 200 ml/cm H_2O and resistances of 2, 5, 10, 50 and 100 kPa litre^{-1} s were used. a = Test compliance; b = test resistance; c = pneumotachograph; d = pressure transducer; e = chart recorder (see text for further details). (Modified from Newton, Hillman and Varley [2].)

after the induction of general anaesthesia for ophthalmic surgery. Measurements were made on 48 occasions in 13 patients breathing spontaneously and on 32 occasions in 13 patients during intermittent positive pressure ventilation (IPPV). Patients' ages ranged from 2 days to 8 yr and their weights from 2.74 to 23.1 kg. Tracheal intubation had been facilitated by suxamethonium in all patients before the measurements. The pneumotachograph and respirometer were positioned within the apparatus deadspace in spontaneously breathing patients with the spirometer inserted to record expired volume, and in the inspiratory limb of the ventilator during IPPV. The pneumotachograph used was a Fleisch flowhead (heated to 37 °C) connected to a Validyne differential pressure transducer (Model MP45). Full details of the accuracy of this recording system have been reported elsewhere [3]. Volume was integrated electronically from the flow signal and results stored on a Racal Store 4 tape recorder for output later on a u.v. paper recorder (SE laboratories, Model 3006). The mean value was taken from five breaths and peak flow rates were noted during each measurement. The accuracy of the system was checked against the Mercury Electronics system using the ventilated test lungs described above. The calibration of the Infanta was confirmed before, during and after the series of studies.

RESULTS

In Vitro

Volume studies. The results obtained with the apparatus shown in figure 2 demonstrated that the Infanta registered volumes from the Starling pump within the range 15–200 ml with an accuracy of ±5%. The registered volume decreased rapidly below 15 ml, whilst over-registration developed rapidly above 200 ml.

Flow studies. The results of the continuous flow studies are shown in figure 3. The response was not linear, but was in principle, similar to that exhibited by any inferential turbine flowmeter. The turbine is required by the manufacturers to respond before the flow exceeds 1.1 litre min^{-1}.

The continuous flow performance of the Infanta turbine was of a nature similar to that established [4] for the standard Wright respirometer, but with more than two and a half times the sensitivity

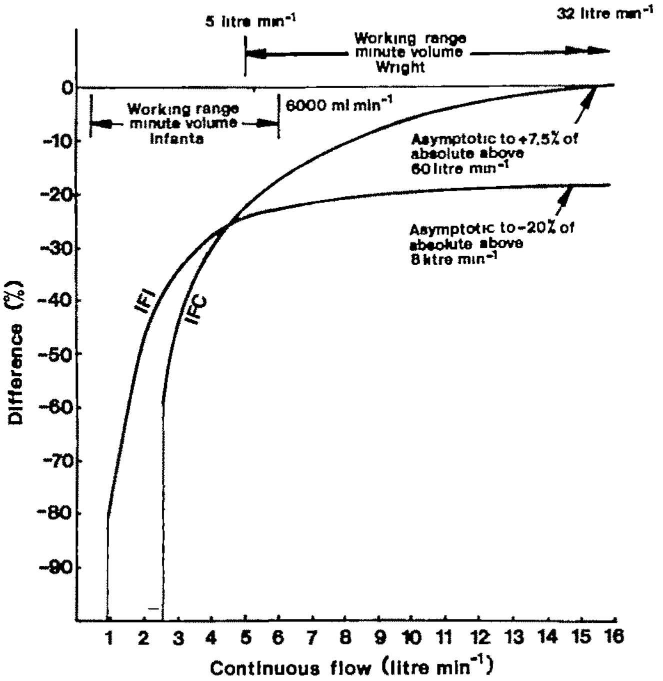

FIG. 3. Percentage difference of registered volume by respirometers (Infanta and conventional Wright turbine) from absolute volume passed at continuous flows up to 16 litre min^{-1}. IFI = initial flow, infanta; IFC = initial flow, conventional Wright turbine.

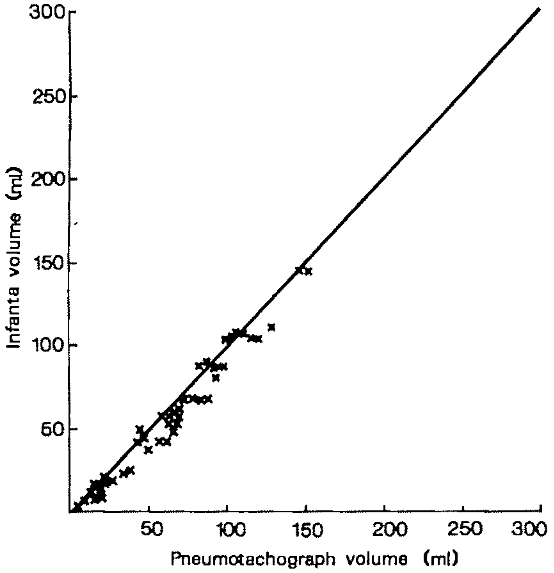

FIG. 4. Comparison of tidal volumes recorded by Infanta respirometer and pneumotachograph during spontaneous ventilation: 48 measuements in 13 children, shown in relation to the line of identity.

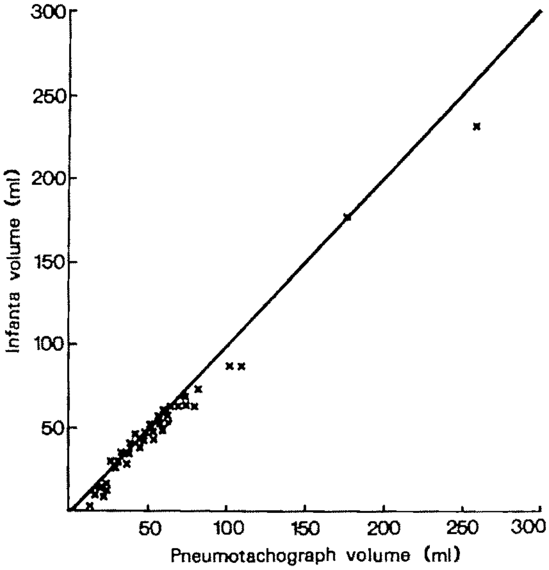

FIG. 5. Comparison of tidal volumes recorded by Infanta respirometer and pneumotachograph during intermittent positive pressure ventilation: 32 measurements in 13 children, shown in relation to the line of identity

overall. The curve is asymptotic beyond 8 litre min^{-1} to 20% less than the absolute continuous flow passing through the instrument. This results from the choice of division of the scales of the instrument already referred to, so that although 400 ml has passed per revolution, the divisions cover 500 ml. The effect is to enhance the reading sensitivity in the ratio of 5:4 by providing compensation of that fixed magnitude overall for what would otherwise appear as under-reading.

In vivo

Tidal volume. Figures 4 and 5 show the results from the respirometer and pneumotachograph in relation to the line of identity for spontaneous ventilation (SV) and IPPV. Plots of the difference between the methods against their mean values are shown in figures 6 and 7. The mean difference during SV was 2.15 ml, with 95% confidence limits for the bias of -0.07 and $+4.37$ ml. The overall 95% confidence limits of agreement between the two methods, when analysed as suggested by Bland and Altman [5] were -9.09 and $+13.39$·ml. During IPPV the mean difference between the methods was 3.08 ± 2.18 ml, and the overall limits of agreement were -7.89 and $+14.05$ ml. Peak flow rates ranged from 1.9 to 20 litre min^{-1}.

The smallest tidal volume recorded by the Infanta was 4.7 ml, corresponding to a measurement of 8.2 ml from the pneumotachograph. This suggests that, as ventilation decreases to the threshold, the instrument under-reads and is, therefore, safe in use.

DISCUSSION

It has been known for many years [6] that, while there is a relationship between minute volume and body weight in infants, this relationship is different for premature as opposed to full-term infants, and that the range of normal data for any particular body weight is large.

Before the introduction of the Infanta respirometer, there had been no reliable mechanical device suitable for the measurement of tidal volume in infants and young children weighing less than 20 kg. Although accurate pneumotachographs are available for this purpose, the complex nature of their calibration procedures, together with the bulk of the equipment, and the problem of drift from the electronic integration of the flow signal, makes it unlikely that they will ever become popular for routine clinical measurement. In addition, it is well known that the resistance of these devices is easily increased by the accumula-

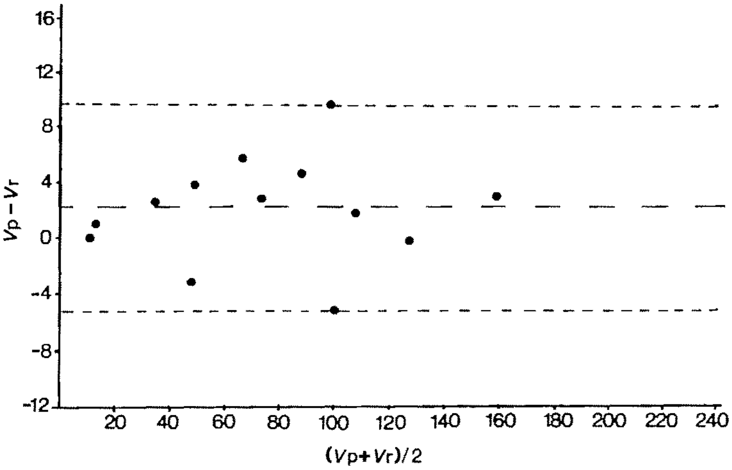

FIG. 6. Difference between tidal volumes obtained with the pneumotachograph (*V*p) and Infanta respirometer (*V*r) plotted against average tidal volume using the two methods. Results in the 13 patients studied during spontaneous ventilation. (Mean ± 2SD lines drawn.)

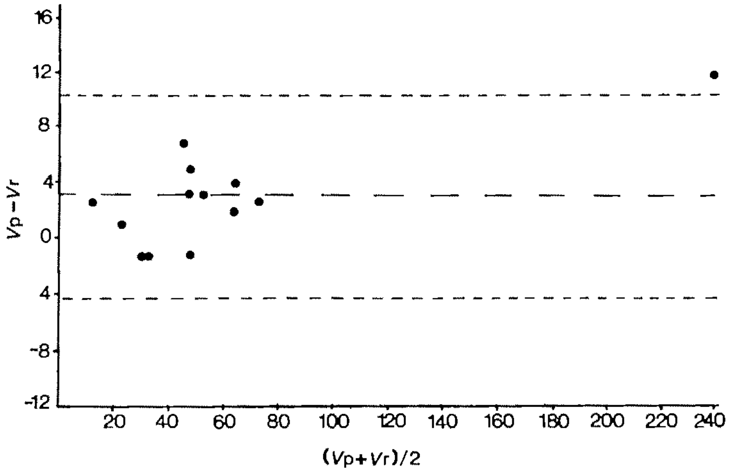

FIG. 7. Difference between tidal volumes obtained with the pneumotachograph (*V*p) and Infanta respirometer (*V*r) plotted against average tidal volume using the two methods Results in the 13 patients studied during intermittent positive pressure ventilation. (Mean ± 2SD lines drawn.)

tion of dirt or the condensation of water vapour on the flow-head. The adult Wright respirometer was thoroughly evaluated by Nunn and Ezi Ashi [4]. They showed that its accuracy was adequate for clinical purposes, a finding which has since been confirmed in more than 20 years of clinical experience. The device, however, under-reads at low flows, such that the lower limit of its accurate working range is at a minute volume of approximately 5 litre. Depending upon the waveform, this represents an error within 10 % at minute volumes greater than 3 litre, 5 % above 4 litre and 3 % above 5 litre. Normal data for minute volume in children [7] show that the adult respirometer will therefore be clinically useful above a body weight of approximately 20 kg.

At the cost of proportionally increasing resistance to gas flow, a reduction in the number and the cross-sectional areas of the slots in the cylindrical stator of the respirometer turbine will increase its sensitivity to a given volume (mass) rate of gas flow. The results of the present study show that the modifications introduced with the Infanta respirometer have increased its sensitivity overall by three times when compared with the standard Wright respirometer, whilst retaining the inherent simplicity and unidirectional flow properties of the traditional respirometer turbine. External size is similar.

Resistance remains lower (0.24 kPa litre^{-1} s at 15 litre min^{-1}) than for other infant respirometers which have been described, and well below the value for non-elastic flow resistance for spontaneously breathing newborn infants [8]. Using Doershuk's data [9], the airways resistance of the largest child in whom this device is likely to be used would be 1.2 kPa litre^{-1} s, about five times the resistance of the respirometer. The modified Wright respirometer evaluated by Wilkes and colleagues [10] had a resistance of 2.9 kPa litre^{-1} s at 18 litre min^{-1} and that produced by Saner and Roth [11] for use in children had a resistance of 0.6 kPa litre^{-1} s at 10 litre min^{-1}. Wilkes and colleagues [10] noted that the resistance of their respirometer resulted in a decrease in minute volume. Milic-Emili and Tyler [12] showed, in adults, that minute volume decreases as non-elastic resistance to breathing increases.

The validity of using ISO test compliances and resistances was demonstrated by Newton, Hillman and Varley [2], whose method also avoids the very difficult problem of asserting and illustrating the wave-forms of the ventilatory flows.

The results of the *in vitro* studies show that the Infanta respirometer registered volumes from the Starling pump with an accuracy of $\pm 5\%$ within the range 15–200 ml. Applying the analysis described by Bland and Altman [5] to the *in vivo* results shows that, although there are between-method differences between tidal volumes recorded by the Infanta and the pneumotachograph, these differences are clinically acceptable. The errors of pneumotachography have been recognized for many years [13–15] and the difficulties of using this technique in the clinical situation are also well known. The Infanta respirometer, being a simple turbine, overcomes some of these difficulties and appears to be at least as accurate as the pneumotachograph. The 14-ml deadspace and rather large bulk make it unsuitable for continuous use within the apparatus deadspace in small infants.

The capability of any turbine type of instrument to measure tidal volumes accurately cannot be deduced from the continuous flow calibration without knowledge of the wave-form for any particular tidal volume. This explains the discrepancies between Infanta and pneumotachograph volumes put forward by Meeke and coworkers [16] when a small range of volumes was delivered from a calibrated syringe at different flow rates. These authors completely ignored the influence of wave-form, although Bushman [17] clearly demonstrated that the relationship between adult Wright respirometer readings and wave-form was far more complex than could be predicted from measurement of peak flow.

The measurements of continuous flow in the present study (fig. 3) demonstrated that volume registration starts at less than 1.1 litre min^{-1} compared with 2.5 litre min^{-1} for the adult turbine. The figure shows the same non-linear response to increasing flow rate when measured under conditions of continuous flow as found for the adult device by Nunn and Ezi-Ashi [4], but with increased sensitivity. Continuous flow data are of use in the initial calibration of new instruments and in recalibration after servicing or repair, but are not analytically readily correlated to tidal volume wave-forms, specifically or in their entirety. No such correlation has been published to date.

For many years neonatologists, paediatric anaesthetists and others involved in the critical care of infants and young children have relied heavily on changes in ventilatory frequency and other clinical signs in the assessment of respiratory failure. Although a few ventilators used in children do contain volume-sensing devices, most machines for paediatric use do not, so that the clinician must rely on chest movement, airway pressure measurements and blood-gas analysis in the assessment of the adequacy of ventilation. Sudden reduction in lung compliance or increase in airway resistance will lead to a reduction in ventilation when pressure generators are used or when there is a deliberately introduced leak in the system, either around the tracheal tube or through such devices as the Newton valve. It is also often difficult to assess the adequacy of ventilation when weaning a young child from ventilatory support. The Infanta respirometer provides useful information which may aid clinical judgement, and the results of this study show that its accuracy for tidal volumes between 15 and 200 ml is adequate for use in these clinical situations.

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ANAESTHETIC EXPERIENCE—THE VIEW FROM BELOW

J. K. MOORE

The Faculty of Anaesthetists has laid down guidelines for the training of registrars and senior house officers in anaesthesia in the *Criteria for Recognition of Hospital Posts under the* F.F.A.R.C.S. *Regulations* [1]. These indicate the range of surgical fields, both basic and specialized, to which the trainee should be exposed, the proportion of time to be spent under direct supervision by a consultant, the need for tuition in regional analgesia and for attendance at more formal teaching programmes within Departments or areas. Although feedback is very important when devising and adjusting a training programme, the actual anaesthetic experience gained by junior anaesthetists throughout their general professional training is not documented. I have kept a record of all anaesthetics administered by me or in my presence and feel that such a record is of value both to the individual and to the Anaesthetic Department. Having commenced Higher Professional Training, I have reviewed the content of my General Professional Training.

METHOD

A logbook was used to record all anaesthetics administered between August 1981, and December 1985. This excludes the first 6 months of my anaesthetic career, but covers four subsequent appointments. The age, sex and hospital registration number of each patient were recorded, as were the surgical procedure performed and the anaesthetic technique used. Preoperative medical conditions were noted. A record was also made of whether the operation was an elective or emergency procedure and whether I was supervised, unsupervised or, latterly, supervising a junior colleague.

SUMMARY

The anaesthetic experience gained during general professional training is reviewed, indicating the spectrum of patients managed and training received. The experience gained was broadly in line with the guidelines recommended by the Faculty of Anaesthetists. The advantage of movement between hospitals at a junior level is noted, as is the value of a case record book, for both the individual and the Anaesthetic Department.

RESULTS

A total of 2625 anaesthetics was administered. Table I shows the spectrum of surgical specialties to which I was exposed. Overall, 70% of the workload consisted of general surgery, gynaecology, obstetrics, orthopaedics and paediatrics, but the proportions varied considerably between posts. I performed a regional anaesthetic block, either alone or in combination with general anaesthesia, on 21% of patients, and these are detailed in table II.

Supervision of elective cases varied from 27% to 43%, but few emergency cases were supervised, reducing overall supervision to 17–36% (fig. 1). In each of my registrar posts, 5–12% of my cases entailed teaching a junior anaesthetist.

Intensive therapy experience was difficult to quantify, although the record of central venous catheterization, pulmonary artery catheterization and minitracheotomy reflects a part of this (table III). In my first three posts, intensive care experience was gained continuously, being included in on-call duties, and daytime attendance averaged one to two sessions per week. In post four, 2 months were spent on a full-time secondment to the intensive care unit. In my first post the on-call anaesthetic staff provided a service for the siting of tunnelled feeding lines, and this is reflected in the number of subclavian lines inserted.

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TABLE I. *Anaesthetic experience*

Specialty	Post 1	Post 2	Post 3	Post 4	Total
Basic experience					
Casualty	53	10	21	1	85
E.N.T.	27	1	62	38	128
General surgery	215	132	104	119	570
Gynaecology	133	52	47	161	393
Obstetrics	180	28	33	94	335
Orthopaedic	125	43	95	42	305
Paediatric surgery	24	74	0	151	249
Specialized experience					
Cardiac surgery	0	0	11	20	31
Dental	3	92	6	79	180
E.C.T.	3	0	38	19	60
Neurosurgery	0	1	5	43	49
Ophthalmology	6	1	0	32	39
Thoracic	25	7	0	1	33
Urology	49	3	38	40	130
Other (cardioversion, maxillofacial, plastic, radiology, radiotherapy)	8	9	16	5	38
Totals	851	453	476	845	2625

TABLE II. *Regional analgesia.* †*Paravertebral, median, ulnar, radial, lateral cutaneous*

Extradural			
Obstetric	253	Ankle	6
Non-obstetric	25	Caudal	17
Spinal			
Obstetric	25	Digital	11
Non-obstetric	79	Femoral	14
Intrathecal morphine	14	Ilioinguinal	48
Spinal drain	5	Intercostal	8
		IVRA	32
Brachial plexus			
Axillary	5	Penile	21
Supraclavicular	8	Sciatic	5
Interscalene	2	Other†	9

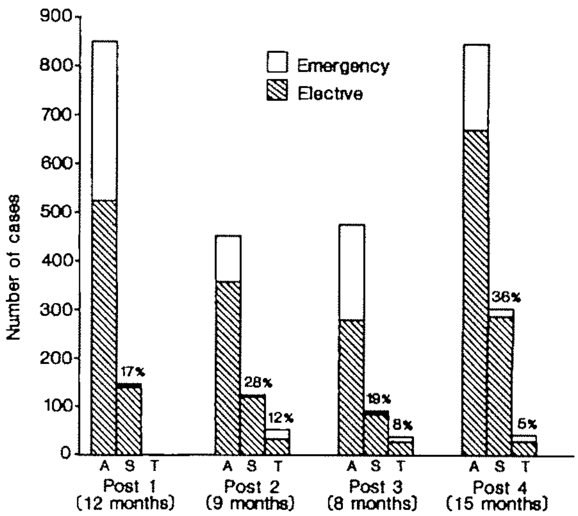

FIG. 1. Histogram of anaesthetics administered in each post (A) showing the number of elective and emergency cases. The number of cases in which I was supervised by a more senior anaesthetist (S) or teaching a junior colleague (T) is also represented. The proportion of supervised or teaching anaesthetics in each post is shown as a percentage of the total in that post.

DISCUSSION

I was encouraged to begin my case record book on moving to my second anaesthetic appointment. I had already spent 6 months in the specialty of anaesthesia within a teaching hospital, where I had been exposed to a wide variety of anaesthetic techniques and surgical specialties; unfortunately I have no permanent record of these. After commencing my record book I held four different appointments before beginning Higher Professional Training. The first post gave me 1 year's experience at senior house officer grade in an English District General Hospital; the second, 9 months at registrar grade on an English teaching hospital rotation, with much of my emergency commitment being as second on-call and, therefore, teaching. The third and fourth posts were in Scotland, the third representing 8 months in a

TABLE III. *Other experience*

Central venous access:	
Subclavian	38
Internal jugular	35
Pulmonary artery catheter	2
Minitracheotomy	3
Bronchoscopy	4
Pericardial tap	2
Chest drain	5
Flying squad (road traffic accident)	3

District General Hospital and fourth as post-fellowship registrar for 15 months in a teaching hospital, with some emergency duties as second-on-call.

When recording a case as "supervised" I included those where a senior member of staff was directly involved in the management of all or part of the procedure, but not those where cover was provided by someone elsewhere on the hospital premises. On occasion, advice regarding emergency cases was sought by telephone, but this was not recorded and these anaesthetics were classed as unsupervised. I recorded as "teaching" those anaesthetics where I was accompanied by and training a junior colleague.

A case was classed as "elective" when it appeared on a routine operating list, and "emergency" when it was booked at short notice, usually by the emergency team, but occasionally added to a scheduled theatre list. An exception to this was the provision of extradural analgesia in labour. Although often provided at short notice, this has been included under elective procedures as the blocks were often instituted during normal working hours and their inclusion under the emergency category would weight the numbers considerably.

A case was only recorded under paediatric surgery if it was performed by a paediatric surgeon, either in a district general hospital (Post 1) or a regional paediatric hospital (Posts 2 and 4). Many more children were anaesthetized in a variety of specialties, including orthopaedics, E.N.T., ophthalmology, plastic surgery, casualty and general surgery. The extremes of age (younger than 16 yr; older than 65 yr) were over-represented when providing anaesthesia for emergency surgery, compared with the numbers met in elective practice. The young and elderly often require different management, even for elective surgery; further compromised by disease, they may pose substantial therapeutic problems when they present as emergencies. It may be that more time should be devoted to the teaching of the particular problems and management of the young and old.

The record of regional analgesia includes only those blocks performed by me, and not those performed under my supervision or for my tuition. Thus more operations were conducted under regional blockade than are represented here.

Supervision was broadly within Faculty guidelines for elective work, which suggest that at least one-third of the junior's theatre sessions should be supervised. This analysis does not take into account the complexity or duration of a case—one supervised thoracic case may represent a complete session, compared with several unsupervised gynaecological cases. In my first post, 144 of the elective cases were extradural blocks for analgesia; of the remaining 381 cases, 37% were supervised. Supervision was, naturally, higher for some specialties than others, reflecting a continuation of the training programme, and this in part explains the increase in supervised cases in Post 4, where more of the work was in specialties such as neurosurgery, cardiac surgery, ophthalmology and paediatrics.

No single post provided complete exposure to all surgical specialties, but over the period the Faculty requirements were well fulfilled, with a broadly-based anaesthetic experience being gained. This demonstrates the advantage of movement between training schemes at junior grades, and also the potential value of a log book to monitor experience and pinpoint deficiencies early in the training period.

The log book is easy to keep up to date, being completed at the same time as the anaesthetic record form. I would suggest that all junior anaesthetists should be encouraged to keep a record book, which is of value for many reasons:

(a) The case record book forms a useful source of ideas for formal and informal case discussions and tutorials. Emergency cases can be discussed at the next teaching session and their management reviewed. The task of remembering an interesting patient for presentation becomes more simple.

(b) Recall of a previously demonstrated technique may not be complete. A written note of drugs, dosage or approach may allow an unusual technique to be used again at a later date.

(c) Deficits in experience become obvious, and representation may then be made for rota changes to minimize gaps in experience and ensure a broad spectrum of training. One may require further exposure to the use of anaesthesia for a specific specialty, experience of particular techniques such as local analgesia or the acquisition of intensive therapy skills.

(d) Regular review of figures may suggest areas of particular importance to the trainee. In my own series the relative excess of emergency cases involving young and elderly patients indicated the emphasis that should be placed on these topics when training junior anaesthetists; teaching would thus be directed towards the situations they are most likely to face alone.

(e) Notes may still be mislaid and, in cases of dispute, an independent record may be beneficial.

(f) Unusual conditions treated some years before can be traced with ease for further follow-up or research.

(g) Finally, experience may be recounted with confidence. This may be helpful (and impressive) when attending interviews.

I could find no reports in the literature of the experience gained during general professional training. "The goal of clinical training is expertise in the care of the patient. Without feedback, mistakes go uncorrected, good performance is not reinforced and clinical competence is achieved empirically or not at all" [2]. Adequate feedback is important for a department when reviewing and revising training programmes. Feedback can also be a useful indicator of how well a given programme is fulfilling its aims and widespread use of the log book within a department may improve teaching and research. Keeping a case record has already been suggested for medical students [3]; it may have clear benefits for the junior anaesthetist.

ACKNOWLEDGEMENT

I would like to thank Dr R. B. Hopkinson F.F.A.R.C.S. for encouraging me to begin my case record book.

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CORRESPONDENCE

ADDITIONAL BLOOD–GAS VARIABLES FOR THE RATIONAL CONTROL OF OXYGEN THERAPY

Corrigendum

Sir,—In our paper on Additional Blood–gas Variables [1] there are important errors in the coefficients given for Equation (1) in Appendix 1. These should be:

$c_1 = 2000$
$c_2 = 2045$
$c_3 = -15$
$c_4 = 2400000$
$c_5 = -31100$
$c_6 = 2400$
$c_7 = -15$

These differ from those given by Thomas [2] (and in our paper) in that the signs of the odd-numbered coefficients have been reversed.

Thomas achieves the same effect by making p (the virtual P_{O_2}) negative. However, this seems to us to be a logical absurdity, and therefore likely to be overlooked—as we did in writing the paper but not, we hasten to add, in performing the calculations. The BBC-Basic function used did give the correct results.

We are grateful to Professor Peter Byles of Syracuse, New York, for drawing our attention to this error and we apologize to readers who have been misled.

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PREVENTION OF PAIN ON INJECTION

Sir,—Pain on i.v. injection of induction agents such as propofol, etomidate and methohexitone continues to be mentioned, but there is a method of relieving this which has been universally successful in our hands, and which is both quick and easy to perform. Before the introduction of the agent in question, 1% lignocaine 2 ml is injected through the indwelling needle, while an assistant maintains an occluding pressure distal to the injection site. After 30 s from the start of the injection, the pressure is released and the induction agent given. With this technique, we have had 100% success rate with more than 100 patients, many of whom have been unpremedicated. This has proved to be a far more effective means of minimizing the pain of these induction agents than other methods tried, such as pre-injection with lignocaine without pressure [1] or mixing with lignocaine [2] and easier than injecting to a fast-flowing drip if one is not already available.

A similar method has been described with etomidate and methohexitone [3]. However, we feel that it is worth reiterating this point with the introduction of propofol, which is an agent ideally suited for induction of anaesthesia in day case surgery, if the injection can be made totally pain fee.

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AN UNUSUAL COMPLICATION

Sir,—It is known that invasive techniques may lead to various complications, as reported in the literature. In certain patients it is difficult to insert correctly the central venous catheters.

During an exploratory thoracotomy, we inserted a 14-gauge central venous catheter to the right subclavian vein, using the direct i.v. technique, without problem. Nevertheless, fluid perfusion was not satisfactory, and we tried several times to reinsert the catheter, without success. During surgical exploration the surgeon confirmed that the tip of the catheter was at the azygos vein.

Because of its rarity, we think that anaesthetists should be aware of this event.

J. Reis
P. Magalhaës
V. N. de Gaia, Portugal

ROUTINE USE OF ATROPINE IN OBSTETRIC ANAESTHESIA

Sir,—We were disturbed that in the recent Postgraduate Educational Issue, Dr Morgan, [1] repeated the old adage that atropine should always be given before the administration of suxamethonium. Whilst accepting that this is true for a repeat dose of suxamethonium, we are unaware of any evidence that a single dose of suxamethonium is likely to cause bradycardia.

This myth was previously widespread throughout anaesthesia, but in the past 20 years the routine use of atropine has virtually disappeared from most anaesthetic practice. However, in some parts of obstetric practice the custom seems to persist, despite the detrimental action of atropine on the lower oesophageal spincter and the particular fear of regurgitation. Our experience in these unpremedicated, emotionally laden, often emergency patients is that tachycardia, not bradycardia, is the norm.

It is almost 10 years since we abandoned the routine use of atropine in our busy (6000 deliveries per annum) maternity unit. There have been approximately 3000 Caesarean sections under general anaesthesia since then and yet no case has made us regret that action. We remain convinced that atropine should not be used routinely in general anaesthesia for Caesarean section.

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R. H. James
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Sir,— Thank you for the opportunity to reply to the letter from Dr May and her colleagues. The standard technique of general anaesthesia for Caesarean section in the U.K. involves an i.v. induction agent, suxamethonium, ventilation of the lungs with 50 % nitrous oxide in oxygen with 0.5 % halothane, and a competitive neuromuscular blocking agent (which, more and more frequently, comprises vecuronium or atracurium). Following delivery of the baby, an opioid analgesic is administered. The use of a sequence of agents such as this, with no parasympatholytic activity, combined with the parasympathetic stimulation of i.p. manipulation has resulted in extreme bradycardia and cardiac arrest [1–4]. (It is noteworthy that the patient described by Milligan and Beer [2] had undergone two previous uneventful laparotomies where the neuromuscular blockers used were gallamine and pancuronium.) It would thus be unreasonable not to recommend the use of atropine under the circumstances described.

The institute in which I work cannot claim the number of Caesarean sections as that of Dr May and her colleagues, but with the above anaesthetic technique and the routine use of atropine, we have seen no bradycardia, no effects that could be attributable to the action of atropine on the lower oesophageal sphincter, and indeed no reason to discontinue its routine use.

M. Morgan
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ATRACURIUM FOR ECT IN PLASMA CHOLINESTERASE DEFICIENCY

Sir,—Dodson [1] described the use of vecuronium in a patient with a possible allergy to suxamethonium, undergoing electroconvulsive therapy (ECT). We describe a case in which low-dose atracurium was used for a patient with plasma cholinesterase deficiency.

A 76-yr-old lady presented with severe exogenous depression. She was treated unsuccessfully with anti-depressant drugs and thus presented for ECT. The patient recalled no problems from a previous cholecystectomy, for which no anaesthetic record was available. There was no other history of any note. Examination showed an aterial pressure of 160/105 mm Hg, but was otherwise unremarkable. Investigations were normal. She weighed 65 kg.

Anaesthesia was induced with methohexitone 60 mg and suxamethonium 30 mg was given to modify the induced fit. Prolonged apnoea ensued. The patient was intubated and ventilated with 100 % oxygen until recovery 40 min later.

Plasma cholinesterase activity was low as measured using suxamethonium as substrate [2]. This was confirmed using a modification of a propionylthiocholine technique [3]. Dibucaine and fluoride numbers were measured by a recently described phenotyping technique [4], and the AF phenotype ($E_1^aE_1^f$ genotype) a provisionally ascribed (table I). Close relatives were subsequently phenotyped and, as shown in table II, gave results consistent with the original phenotype. The AF phenotype is known to result in prolongation of suxamethonium apnoea [5].

Atracurium at a dose of 10 or 15 mg was used for muscle paralysis, during subsequent treatments. Anaesthesia was induced with methohexitone 50 mg, with increments of 10 mg as deemed necessary for maintenance. One hundred percent oxygen was given by intermittent positive pressure ventilation via a Mapleson C breathing system using a mask and airway. ECT was given 4–7 min after induction, when maximal block had occurred, as judged using a peripheral nerve stimulator. Muscle paralysis was antagonized using atropine 1.2 mg and neostigmine 2.5 mg or atropine 0.84 mg and edrophonium 40 mg, 10–12 min after ECT. Recovery was monitored by

Table I. *Concentrations, values and ranges for incubation with various substrates: Sux. = Suxamethonium at 37 °C; Prop. = propionylthiocholine at 37 °C. Dibucaine number is with benzoylcholine at 25 °C; Fluoride number is with benzoylcholine at 25 °C*

	Sux. (u. litre^{-1})	Prop. (Ku. litre^{-1})	Dibucaine No.	Fluoride No.
Patient	18	1.8	45	31
Range	> 60	> 5.0	78–85	55–65

TABLE II. *Genotype results of patient and relatives*

Patient	$E_1^aE_1^f$
Daughter	$E_1^uE_1^f$
Granddaughter	$E_1^uE_1^f$
Granddaughter	$E_1^uE_1^u$
Brother	$E_1^aE_1^f$
Sister	$E_1^aE_1^f$

train-of-four on a peripheral nerve stimulator and sustained head lifting.

General anaesthesia for ECT has three main functions: lack of awareness of the therapy; modification of the motor effects of the fit to prevent injury; fast recovery of reflexes and consciousness enabling early airway protection. Suxamethonium is the best neuromuscular blocking drug for ECT, because of its short duration of action which permits rapid return of laryngeal reflexes and ventilation.

Plasma cholinesterase deficiency causing prolonged apnoea following suxamethonium is well known [5]. Atracurium has been used in a patient with severe hepatic disease, who had low plasma cholinesterase activity, without prolongation of its effect [6].

In this patient, atracurium was successfully used to modify the motor effects of ECT, as judged clinically. Antagonism of the neuromuscular blockade with anticholinesterase was successful at the end of the procedure without any ill effects. We would therefore recommend that atracurium in low dosage is a suitable alternative to suxamethonium for ECT in a patient with plasma cholinesterase deficiency.

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PLASMA PROLACTIN CONCENTRATIONS DURING HIGH-DOSE OPIOID ANAESTHESIA

Sir, – Among other hormones [1], prolactin is one of those of which the concentration increases as a response to surgical stress [2]. Since narcotic analgesics also induce an increase in basal plasma prolactin concentration [3], the significance of prolactin as an indicator of stress under the influence of opioids is obscure.

We reported in this Journal [4] plasma concentrations of three hormones regarded as indicators of stress (cortisol, β-endorphin immunoreactivity and arginine vasopressin) during cardiac surgery under fentanyl or alfentanil anaesthesia Since we considered it interesting to know if changes in the level of stress observed during high-dose opioid anaesthesia could be reflected in changes in plasma concentrations of prolactin, we measured prolactin concentrations in the stored samples obtained from the patients of our previous study.

As previously described [5], nine patients received fentanyl and 10 alfentanil as a combination of a loading dose and a continuous infusion for coronary artery bypass grafting. At certain predetermined stages of anaesthesia (fig. 1), blood samples were drawn from the radial artery, for the determination of plasma prolactin concentrations by radioimmunoassay [6] and for the analysis of plasma fentanyl/alfentanil concentrations by capillary gas chromatography [5].

Analysis of variance with repeated measures design was used for statistical evaluation of intra-group changes. Dunnett's corrections were used for subsequent multiple comparisons by the paired *t* test. The *t* test for two independent samples was used to compare changes between the groups. The linear regression analysis was used to assess the interrelationship between prolactin and fentanyl or alfentanil concentrations. Because women are known to have higher baseline concentra-

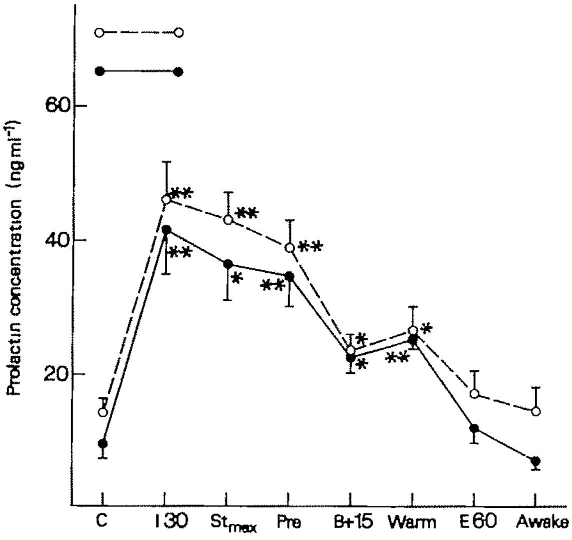

FIG. 1. Plasma prolactin concentrations in 16 men during high-dose fentanyl (○) or alfentanil (●) anaesthesia (mean values ± SEM). C = control value before induction of anaesthesia, I30 = 30 min after initiation of induction of anaesthesia; St_{max} = maximal sternal spread; Pre = immediately before CPB; B + 15 = 15 min after initiation of CPB; Warm = after rewarming at the end of CPB; E60 = 60 min after discontinuation of opiate infusion; Awake = awakening from anaesthesia. Significant changes within the group: *$P < 0.05$; **$P < 0.01$.

tions of prolactin and more pronounced responses to noxious stimulation than men [2], we separated the sexes when analysing the prolactin concentrations to assure that the distributions of the prolactin data were normal.

The plasma prolactin concentrations of the 16 men (eight in either group) of our 19 patients are shown in figure 1. In both groups of men, plasma prolactin had increased significantly 30 min after the start of induction of anaesthesia. Thereafter, prolactin concentrations remained almost unchanged during surgery until the commencement of cardiopulmonary bypass (CPB). During CPB, plasma prolactin concentrations were 10–15 ng ml^{-1} smaller than those immediately before CPB, but differences from the awake control value were still statistically significant. During recovery from anaesthesia (60 min after discontinuation of the infusion of opioid and at awakening from anaesthesia) plasma prolactin concentrations decreased further and no longer differed significantly from the control values. No significant differences were observed between the two study groups at any stage of the study. The pattern of the responses with the three women subjects were more pronounced (peak concentrations, 100–194 ng ml^{-1}, were measured at I30 or St_{max}) than with men.

Statistically significant correlations were observed between plasma prolactin and fentanyl concentrations ($n = 64$, $r = 0.68$, $P < 0.001$) and between plasma prolactin and alfentanil concentrations ($n = 64$, $r = 0.58$, $P < 0.001$) in the male patients.

The pattern of increase in prolactin concentration found in the present study was consistent with that in the previous studies in cardiac surgical patients under fentanyl [7] or sufentanil [8] anaesthesia. Thus, the prolactin response was most prominent during the induction of anaesthesia and early surgery and less pronounced during and after CPB. We found a significant correlation between plasma prolactin and fentanyl or alfentanil concentrations. Thus, the present study seems to provide further evidence of the stimulatory action of the opioids on prolactin secretion [3]. On the other hand, because increased plasma prolactin concentrations have been measured under halothane anaesthesia [7], neuroendocrine mechanisms in the regulation of prolactin release unaffected by opioid regulation may also be involved in anaesthetized patients [9].

The behaviour of prolactin in our patients differed totally from that of other stress indicators (cortisol, β-endorphin immunoreactivity and arginine vasopressin) as published in our previous study [4]. Prolactin appeared to be a hormone which does not indicate the degree of stress during cardiac surgery.

Our results suggest that the changes in plasma concentrations of prolactin during high-dose opioid anaesthesia for cardiac surgery reflect changes in the plasma concentrations of opioid anaesthetics rather than changes in the degree of stress. The major conclusion from this study is that plasma prolactin concentration cannot be regarded as an indicator of stress during cardiac surgery under high-dose opioid anaesthesia.

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BOOK REVIEWS

Neurosurgical Anaesthesia and Intensive Care, Second Edition: By T. V. Campkin and J. M. Turner. Published (1986) by Butterworths. Pp. 323; indexed; illustrated. Price £40.00.

The second edition of this popular book follows the same format as the original with only a few alterations and it can be safely predicted that it will be another success.

It will be a disappointment to many that the chapter on induced hypothermia has been excluded. The authors make frequent reference to the technique but a full chapter, including history, would have been more acceptable, since there is still considerable interest in hypothermia in the United Kingdom.

Much of the chapter on induced hypotension is historical, but is still of interest to the diminishing number who practise the technique in neurosurgery. The authors draw attention to the usefulness of isoflurane as a hypotensive agent because of its peripheral vasodilator effect while maintaining cardiac output in the same way as sodium nitroprusside but, in addition, they note that it produces profound metabolic depression in modest doses as well as favourable effects on the cerebral energy state. Therefore, it would appear to be the ideal agent with which to induce hypotension in most situations while providing a considerable degree of cerebral protection. Indeed, some may ask if there is ever any need for the administration of i.v. non-anaesthetic hypotensive agents in neurosurgery. Some discussion on the indications for hypotension in aneurysm surgery would have been welcomed. Profound hypotension has largely been abandoned and nowadays surgeons prefer to occlude the feeding vessels before clipping the neck of an aneurysm. In these circumstances, it would be important to maintain adequate cerebral perfusion. In pituitary surgery, one would have to be cautious about inducing hypotension to a mean arterial pressure of 50 mm Hg in circumstances in which the chiasmal circulation may be comprised. Others may question the need to induce hypotension in spinal explorations in the prone position; surely, the main problem here is venous bleeding. It is difficult to comprehend the reason for the suggestion that trimetaphan or sodium nitroprusside be used to induce hypotension to systolic arterial pressure less than 90 mm Hg in these patients and, in the case of trimetaphan, without intra-arterial pressure monitoring. Many would disagree with this.

The authors obviously felt that it was important to discuss the pharmacophysiology of drugs such as Althesin or etomidate which have been withdrawn or have limited use. It would certainly be a great pity if future neuroanaesthetists were deprived of an exposition on the elegant experimental work on these agents which emanated from the Leeds School. There is no mention of alcuronium, and the authors are dismissive of the opioid, phenoperidine, both of which drugs are still popular in neurosurgical anaesthesia. They report the release of histamine as being a factor in causing cerebrovasodilatation when discussing tubocurarine; this could be a reason for the occasional increase in intracranial pressure which is seen with phenoperidine. Many neuroanaesthetists in the United States avoid or limit the use of nitrous oxide during craniotomy and some discussion on this would have been welcome.

The last three chapters on paediatric anaesthesia, intensive care and the management of head injuries are outstanding and reflect the wide experience of the authors.

The book is comprehensive and any aspiring neuroanaesthetist would have little difficulty in reading the background literature to a particular problem. However, there are too many references which would be well nigh impossible to trace. Inevitably, there is repetition, but in some ways this is commendable and avoids the tedium of jumping from one reference list to another.

Unfortunately, there are several typographical errors; the "impaired" electron on an outer orbit must surely be "unpaired." There was one factual error. Takeshita and his colleagues did not describe an increase in cerebral metabolism with ketamine in man; they observed no change and went on to demonstrate, in dogs, that the cerebrovasodilator action of ketamine was in part attributable to the blockade of the transmembrane influx of calcium at cellular level.

There is much of interest in this book for practitioners in all branches of the neurosciences and it will be invaluable to anaesthetists about to embark on their first neurosurgical rotation. It is mainly a personalized account and, although the techniques and choice of drugs are in most cases admirably reasoned, it is doubtful it if will become the standard work on neuroanaesthesia.

J. Barker

Anesthesia and Organ Transplantation. Edited by S. Gelman. Published (1987) by W. B. Saunders Co. Pp. 254; indexed; illustrated. Price £45.00.

This book is edited by Dr Gelman of the University Hospital, Birmingham, Alabama and the majority of the contributors are members of the same department. The first section discusses the Immunological Aspects of Tissue Transplantation and there is an interesting portion on the reasons for and the benefits of pretransplantation donor-specific blood transfusion. The second section, which is entitled Brain Death and Ethics of Organ Transplantation, discusses the theological and legal considerations and the criteria for brain death. Three sections which describe the metabolism and preservation of organs targetted for transplantation, immunosuppressive therapy and infection are of interest, but are not to be expected in a book with this title. The sixth chapter deals with Kidney Transplantation although, unfortunately, only a small proportion deals with the choice of anaesthesia for the transplant recipient; the remaining pages of this section describe the anatomy and physiology of the kidneys, the live and cadaver donor, surgical techniques, complications and results of renal transplantation. There is a good chapter on Heart and Heart–Lung Transplantation by Drs Wynne and Finch from

Stanford which not only includes descriptions of anaesthesia for both procedures, but also describes the problems of anaesthesia for unrelated operations on cardiac transplant recipients. The section on Liver Transplantation describes the anatomy and physiology of the liver, together with the pathophysiology and pharmacokinetic implications of liver disease. There is also a comprehensive account of the anaesthetic management of the recipient, including the preoperative assessment of these patients and their postoperative care.

It may seem strange that, in a book devoted to anaesthesia and transplantation, there is no mention made of corneal or pancreatic transplantation, whereas two sections are the subject of replantation of severed limbs and skin transplantation, and a further section is entitled Blood Transplantation—Blood Transfusion.

The book is well produced, it has good references ranging from 1742 to 1986, but the tables are similar to the curate's egg and many of the illustrations are poor. It is obviously aimed at the North American market and the individual anaesthetist would not be advised to purchase a copy—although it might merit space on the shelf of a Department involved in transplantation procedures.

I. T. Davie

Anaesthesia Review 4. Edited by L. Kaufman. Published by Churchill Livingstone. Pp. 234; indexed; (minimally) illustrated. Price £14.95.

The predictably rapid appearance of the fourth book in this series is testimony to Dr Kaufman's industry, and to the fact that he is producing a volume of use to many anaesthetists.

The book contains 21 chapters by 21 authors, some chapters being contributed by two authors. A short introductory chapter commemorates the 140th anniversary of the first public demonstration of ether in the U.K. Recent medical advances relevant to anaesthesia are then reviewed by Dr Kaufman and almost 100 references are supplied.

Three respiratory chapters start with a consideration of anaesthesia and asthma. This contribution suffers from being written by a non-anaesthetist, listing potential hazards, but giving little positive advice. In particular, postoperative analgesia by opioids is stated to be hazardous, and this advice is given in a manner that is inappropriate for the majority of asthmatic patients undergoing surgery. Regional blockade is dismissed, using a reference that does not corroborate the statement made, and other references are rather dated. Treatment of acute, severe asthma is considered by two authors, one a physician, the other an anaesthetist. The first part of this chapter is clear and concise and would promote confidence in anyone dealing with severe asthma. The later consideration of artificial ventilation is less well written. High frequency ventilation is a large topic and, of necessity, each section is brief. This chapter is well laid out and would be useful for examination candidates

Five chapters are devoted to the cardiovascular system. Drugs used to treat hypertension, in particular recently-introduced agents, are soundly covered. A well balanced consideration of hypotensive anaesthesia is followed by two chapters on antiarrhythmic drugs and common cardiac arrhythmias. Arrhythmias are considered in the context of myocardial infarction. Their management in other situations, for example in relation to anaesthesia and surgery, or poisoning, would have improved this contribution. Selected aspects of anaesthesia and postoperative care for cardiac surgery are covered in a manner most suited to the examination candidate.

The endocrine response to surgery is comprehensively reviewed. Two chapters on paediatric anaesthesia and intensive care consider, initially, fetal development, preterm physiology and some aspects of intensive care management. The anaesthetic implications of recent research into intraventricular haemorrhage, apnoea and sudden infant death syndrome are then expertly covered.

The second contribution from the U.S.A. concerns advances in trauma emergency care. The content of this chapter is excellent and is matched by the up-to-date and definitive reference list.

A review of cases reported to the Medical Protection Society over the past decade is the basis for a chapter on medico-legal aspects of anaesthesia.

A short, informative chapter on anaesthesia and laser surgery discusses the different lasers in medical use. Laryngeal surgery using a carbon dioxide laser is the most hazardous situation and is thoroughly covered. The authors's preferred anaesthetic technique is outlined and justified.

The use of narcotics in general anaesthesia is inexplicably separated from a contribution by Dr Kaufman on pain which reviews opioid receptors and considers newer routes of administration of these drugs.

An excellent chapter on recovery from nerve blockade gives a clear outline of the possible mechanisms of action of anticholinesterases and the clinical implications. Dr Kaufman concludes with two chapters updating previously reviewed topics.

This book continues an excellent series. It should be emphasized that one of its major attributes is the list of over 1000 recent references. Some chapters would benefit from illustrations, but the overall content is very good. I have no doubt that Review 5 is being assembled and will be welcomed.

A. Lee

Anesthesia, Second Edition. Edited by R. D. Miller. Published (1986) by Churchill Livingstone. Pp. 2419; indexed; illustrated.

When the Editor of the *British Journal of Anaesthesia* put out the first edition of *Anesthesia* for review he decided to ask two independent reviewers each to consider volumes 1 and 2 separately. However, this second edition is larger by 890 pages and the inclusion of 11 new chapters and, as it now appears in three volumes, the task of review is even more complex. There are now over 2419 pages divided into 68 chapters from 70 contributors. The present three reviewers working in one department have, nevertheless endeavoured to consider the book as a whole and not as three separate texts.

After its publication in 1981 *Anesthesia* rapidly became established as the definitive text on the subject supplanting, outside the United Kingdom at least, the older established British textbooks. There are basically 10 main sections to the book which encompass all aspects of the subject, which are grouped as: Introduction; Scientific Foundations of Anesthesia; Preparation of the Patient and Use of Anesthetic Agents; Preoperative, Intraoperative and Regional Analgesia (three separate sections); Physiological Function during Anesthesia; The Systems and Specific Areas; Specific Anesthetic Problems and/or Techniques; Consultant Anesthetic Practice; Critical Care Medicine. In addition to a general text revision, the chapters new to this edition comprise material on anaesthetic history; medico-legal matters; the scientific basis of anaesthesia; and a much more extended account of critical care medicine.

For the most part the chapters are written by authorities in their own fields. However, the authors are drawn entirely from centres in the United States of America. The book suffers from the two main drawbacks of any multi-authored text, namely, individual chapters vary in their lucidity and comprehension and there is a degree of repetition. However, it is probably fair to state that these are not more marked here than in most multi-author books and it is plainly impossible for a book of so comprehensive a nature to be the work of a mere handful of people. The strong points of *Anesthesia* are that it is well referenced and very comprehensive. Practically anything the anaesthetist may want to look up can be found in this book. However, it is awash with irritating mistakes and misprints which in certain situations would make the basic concept almost impossible for the newcomer. Just a few examples: it is stated to be the charged form of local anaesthetic that most readily diffuses across neural sheaths (p. 998); in the worked examples of determining base excess it is stated that the pH should be returned to 7.0 by decreasing $P\text{co}_2$ (p. 1298); and in the account of the measurement of closing capacity, the contributor appears to forget that he is describing the tracer gas technique and drifts on to a conclusion of the description of the nitrogen wash-out technique (p. 1130). Figure 48–4 on p. 1735 in the chapter on resuscitation of the newborn is confusingly labelled with 13 identification letters, none of which are explained in either the legend or the text. However, the same figure turns up again as Figure 49–7, this time minus the "identification", on p. 1775 in another chapter on paediatric anaesthesia by the same contributor. All this can be very confusing for the student. However, the chapter on paediatric anaesthesia includes some very useful case reports. It is of course understandable that errors will inevitably occur in a work of this size, but the occasional mis-spellings of Magill and Macintosh (as McGill and MacIntosh) jar on the British reader.

In conclusion, this is a very large and comprehensive, but very American, account of the subject. Some of the practices recommended are uniquely American and thus it is unlikely that *Anesthesia* would become the primary standard text in the United Kingdom; in addition, the English textbooks are less expensive. *Anesthesia* is nevertheless strongly recommended as a useful and generally easy to read reference text book and permits a most useful comparison between thoughts on clinical practice on both sides of the Atlantic. It should be available in every departmental library as a good and up-to-date source of material. For the next edition we hope that the editor will take the knife more ruthlessly to some of the more longwinded contributions, cut down on the long lists which appear in some of the tables, and get rid of the far too many very irritating, simple mistakes.

A. P. Adams
R. M. Jones
K. J. Wark

Cardiovascular Problems in Paediatric Critical Care. By D. B. Swedlow and R. C. Raphaely. Published by Churchill Livingstone. Pp. 311; indexed; illustrated. Price £35.00.

This book is the latest addition to a series of volumes on "Clinics in Critical Care Medicine". The opening chapter contains an excellent and detailed review of cardiovascular physiology. If there is a criticism of this chapter, it is that it is too long—80 pages out of 300 pages in a book intended for clinicians.

Included in the chapter on non-invasive assessment is a short but good description of some of the more subtle clinical features associated with failure of the circulation. Many other textbooks do not give sufficient emphasis to, or overlook, this important aspect of assessment.

The chapters on anaesthesia, manipulation of the circulation and resuscitation provide the reader with state-of-the-art accounts of the practical management of these patients.

This is an outstanding book which contains a wealth of information and practical advice. The authors have succeeded in their objective to "present current information in a form that is both useful and convenient".

M. Scallan

Companion to the F.F.A.R.C.S. Part III. By C. F. Corke and I. J. B. Jackson. Published by Blackwell Scientific Publications. Pp. 183; indexed. Price £9.50.

This paperback is aimed at candidates sitting the final F.F.A. (Although some parts would be appropriate for the Part I examination) and is intended primarily as a revision text.

Section one gives readers, in short note form, a set of model answer plans which can be used for viva or essay questions. Although some 90 topics are covered in just over 100 pages, the content is not, nor is it intended to be, comprehensive. The headings follow no particular order, although each subject is neatly and logically presented. Despite being simplistic in places, the text has useful summaries of a range of conditions, treatments and agents. However, in the anatomy section, I question the value of six pages on the trigeminal nerve at the expense of an adequate description of the larynx.

Section two gives guidance on answering questions during the clinical examination, with the main emphasis on the interpretation of the ECG and chest x-rays. There is nothing here that could not be found in other texts, although the information is, perhaps, more simply and clearly laid out.

Section three contains 10 sets of questions to give new candidates some idea of the potential scope of the viva. The questions are wide ranging and could form the basis for mock vivas between candidates.

Section four is five pages long and contains 29 references considered by the authors to be important source documents. The choice is a little arbitrary and fails, for instance, to mention the first use of curare, while including the early use of nitroprusside.

Overall, my impression of this book is mixed. It has the air of being put together from the revision notes and examination memoires of a diligent candidate and is, in places, too simplistic. On the other hand, the text encourages a structured approach to answering questions and contains much useful revision material, simply and succinctly presented. This book will not appeal to everyone, but many candidates will find it a valuable *aide-memoire* before sitting the F.F.A.

D. Paul

Papers for publication and all editorial communications should be addressed to the Editor, University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW; business communications to the publishers: Professional & Scientific Publications Ltd, BMA House, Tavistock Square, London WC1H 9JR.

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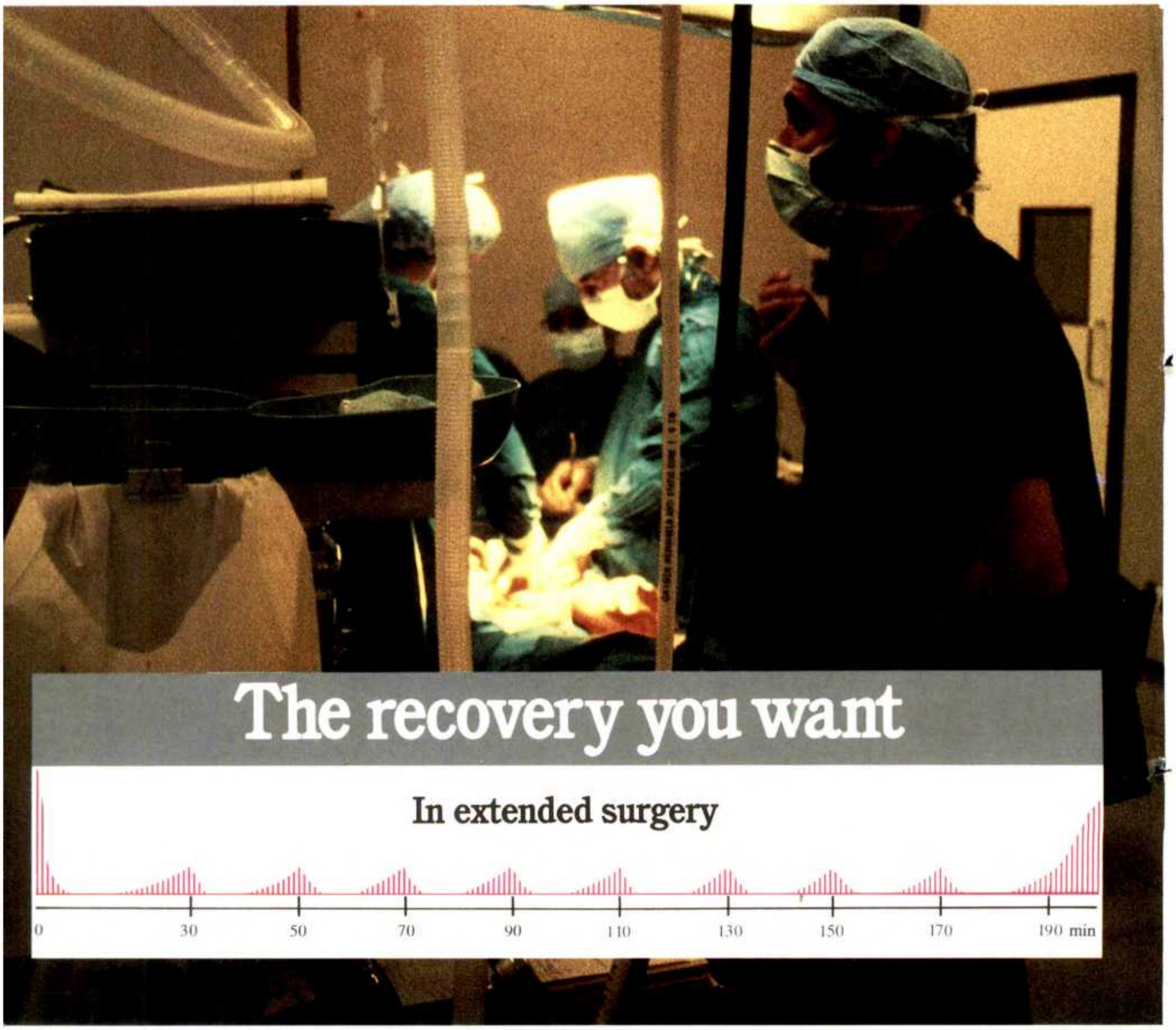

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1. Data on file, Wellcome, 1987.
2. Yate, P.M. *et al.* (1986), *Br. J. Anaesth.*, **58**, 112 S.

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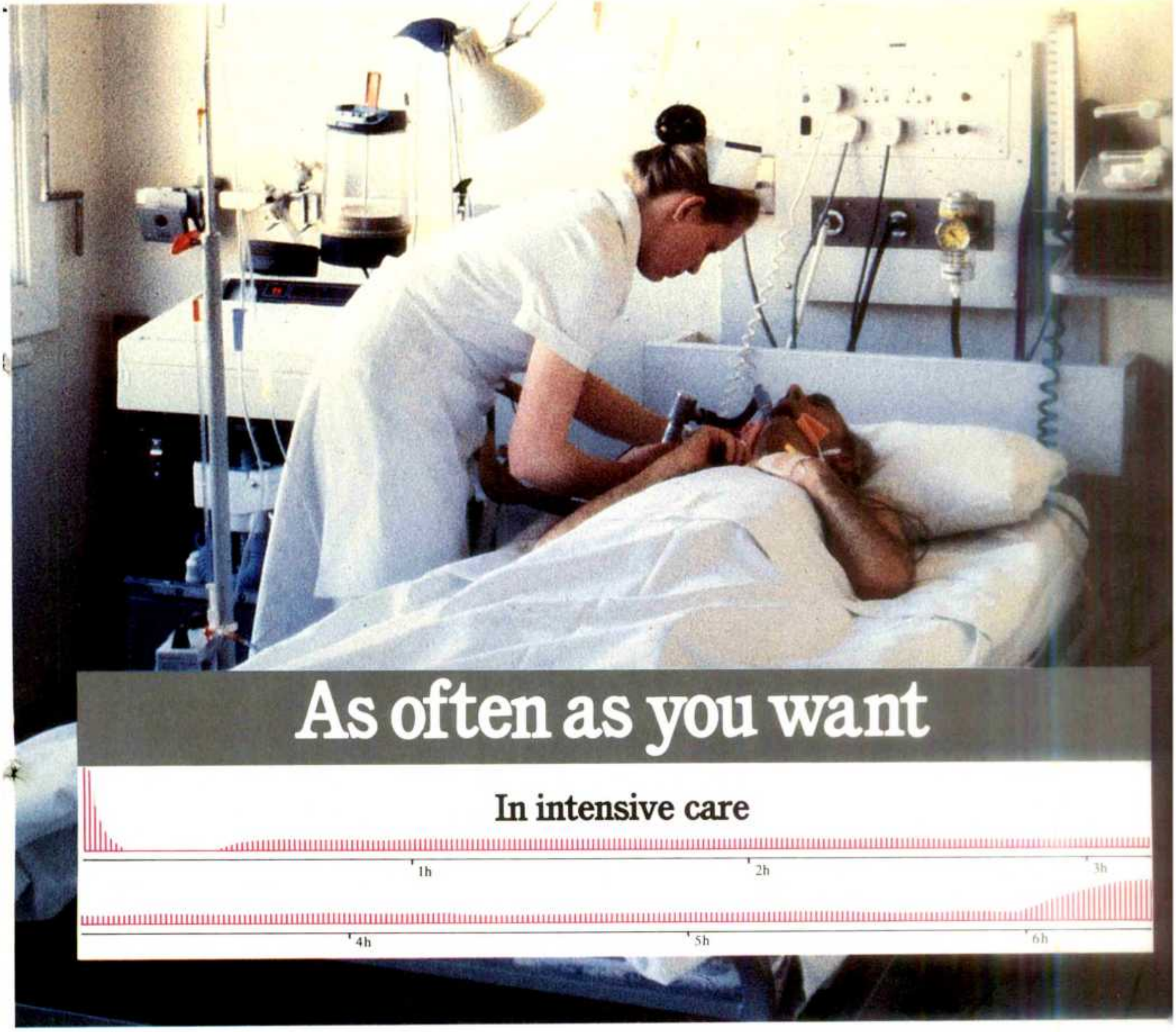

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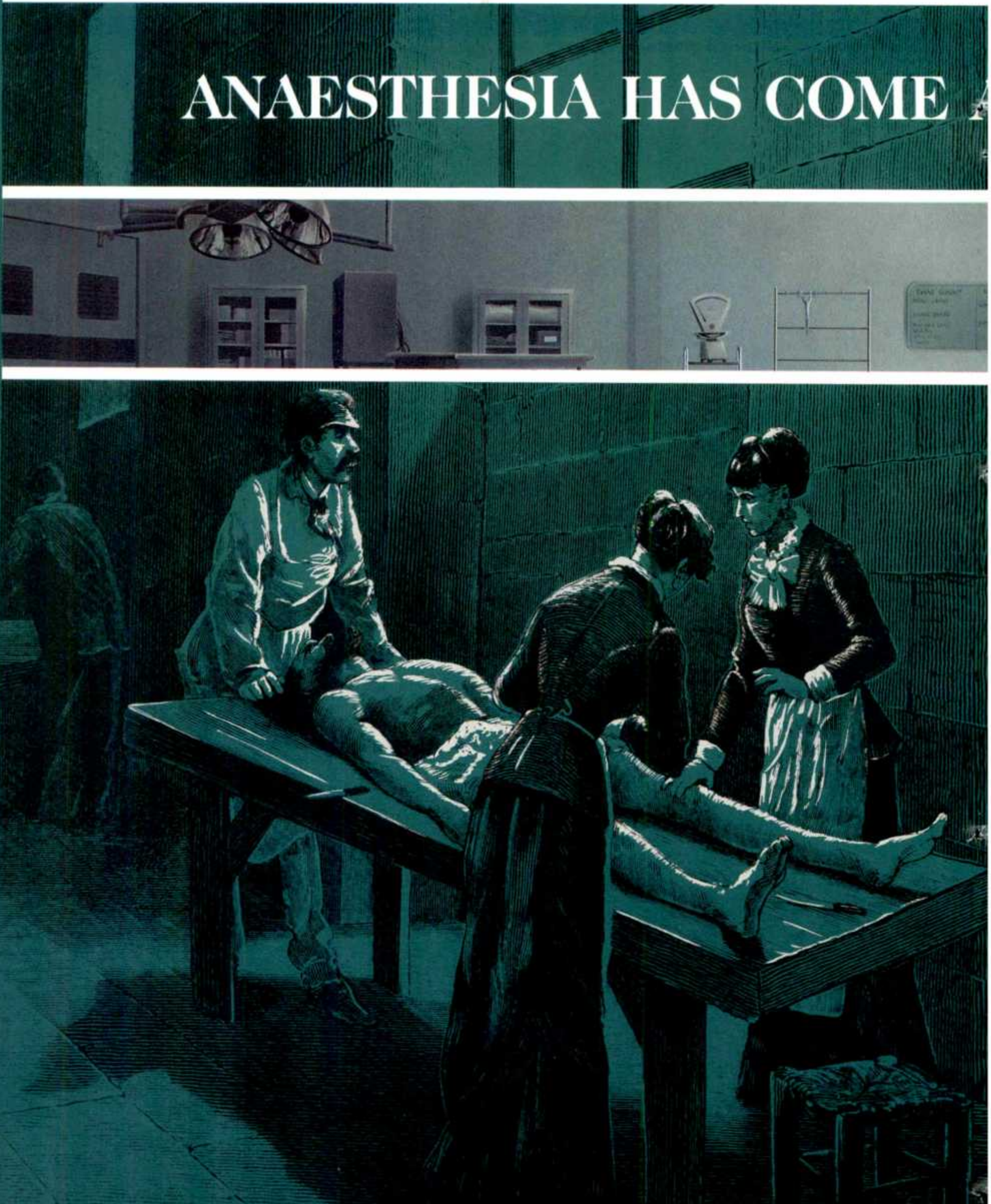

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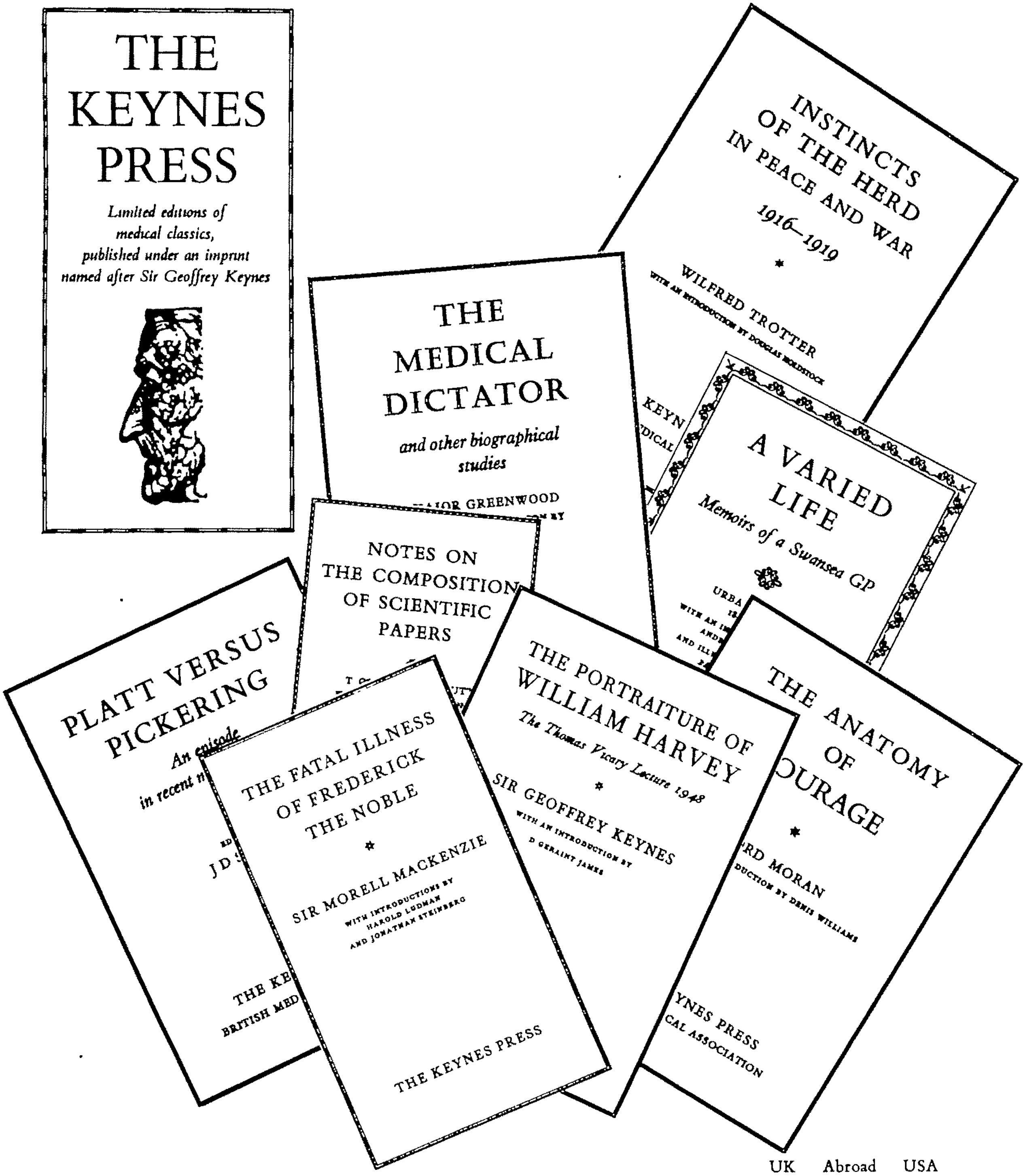

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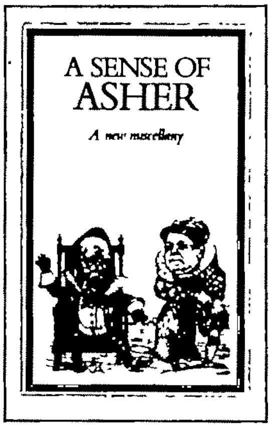

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BRITISH JOURNAL OF ANAESTHESIA

VOLUME 60, No. 3 FEBRUARY 1988

EDITORIAL

THE DIAGNOSIS OF MH: ITS SOCIAL IMPLICATIONS

Seventeen years ago at the first international meeting concerned with MH, held in Toronto [1], there was optimism that this newly recognized condition would be rapidly understood and that the mortality would decrease from over 70% to zero. Good progress towards this ideal has been made, but the original, clearly circumscribed field of MH now has blurred perimeters: anaesthetists and others are concerned with possible associations between MH and overt primary muscle disease (especially Duchenne MD and myotonic dystrophies), with hyperthyroidism and thyroid crisis, with Neuroleptic Malignant Syndrome (NMS), and with Sudden Infant Death Syndrome (SIDS). Is it possible that MH is such a heterogenic ragbag of otherwise unrelated conditions, or is it a specific genetic disease? The papers by Brownell and Harriman in this issue address this problem and their conclusions tend to support the latter view. If MH proves to be a clearly defined pharmacogenetic disease, there must be a similarly clearly defined pathogenesis. Gronert and co-workers have summarized a complex subject, and pay tribute to the recent demonstration by Lopez and colleagues [2] of the central role played by intracellular ionic calcium.

Whilst the clinical and biochemical aspects of MH have been widely debated over the past quarter of a century, little has been said of the social implications. Relevant to this is the use of the abbreviation MHS, which was introduced by the European MH Group [3] to indicate an individual assumed to be susceptible (or genetically predisposed) to MH when placed in a "triggering" environment. MHS is not a disease, but a label resulting from a laboratory investigation. The strength or weakness of the MHS label depends on the strength or weakness of the laboratory tests, as most MHS individuals will not have had an MH episode themselves. The European MH Group was formed in 1983 to encourage standardization of the test procedure throughout Europe, and has been largely successful in this. There is as yet no similar standardization of tests in North America, where "MH susceptible" means different things in different departments.

It is to be hoped that any anaesthetist would react positively when he learns a patient is MHS, and provide safe anaesthesia, but when the MHS label was first devised it was not realized that others would react positively to it, such as future employees, promotion boards and even potential spouses (in Japan the possession of a genetic defect can seriously hinder a person's ability to find a marriage partner).

Although providing safe anaesthesia for MHS individuals is straightforward, a strong case could be made to exclude MHS subjects from particularly physically stressful occupations such as armed combat, which inevitably result in a need for anaesthesia in less than ideal circumstances, or environments containing chemicals known to cause MH, such as the dry cleaning industry. It is very doubtful if exposure to chemicals at school or anaesthetics in a nursing or medical environment could trigger MH.

The main concern expressed by MHS individuals and their families is the way their condition is disregarded by some hospital doctors and some GPs. MH susceptible patients do not have their fear of anaesthesia relieved by an obstetrician saying, smoothingly, "There is nothing to worry about" when there has already been an MH death in the near family. MHS patients know there *is* something to worry about, and usually understand what. They have a particular fear of illness developing during foreign travel. It is possible to provide them with a list of centres of MH excellence within Europe—but further afield this becomes more chancy.

The diagnosis of MH carries with it an important obligation to warn other members of the family of a potential anaesthetic hazard. It is not acceptable now to make a provisional diagnosis of MH and merely to warn the patient. The diagnosis needs to be substantiated by *in vitro* muscle testing, and other family members offered the investigation as appropriate. Failure to act in this way could result in a fatal MH episode in another family member. Sadly, as community physicians, who are ideally placed to co-ordinate such a family study, have not grasped the nettle offered them [4], and as geneticists do not carry out the screening investigations themselves, anaesthetists are left with this responsibility.

The most crucial part in this sequence is to make a provisional diagnosis. It could be argued that the fulminant classical MH mentioned by Rosenberg, and explained in biochemical terms by Heffron in this issue, should be a thing of the past as it represents both a failure of basic monitoring and a failure to react to obvious warning signs such as persistent and progressive tachycardia, increasing $P\mathrm{E}'_{\mathrm{CO_2}}$ and increasing body core temperature. It would be quite impossible to investigate by muscle biopsy all patients who react idiosyncratically to suxamethonium. Evidence is accumulating that suxamethonium frequently causes an increase in jaw tone [5, 6]. For a realistic provisional diagnosis of MH to be made, corroborative evidence of MH should be sought at the time of the episode—this includes measurement of blood-gas tensions and pH, and serum potassium and CK concentrations at the time and 12–24 h later, and urinalysis for myoglobin in the first voided specimen.

The mortality from MH in the United Kingdom has remained unacceptably high, at around 24% of diagnosed cases [7]. If there has been a recent decrease, it certainly has not plummeted as Harrison predicted with the introduction of dantrolene in 1980. MH can no longer be thought of as an "Act of God". All anaesthetists have heard of it and it is hoped this issue will help to raise the level of understanding to safeguard patients (and indirectly ourselves) from a readily detectable and treatable condition.

F. Richard Ellis

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Br. J. Anaesth. (1988), **60**, 253–267

AETIOLOGY OF MALIGNANT HYPERTHERMIA

G. A. GRONERT, J. MOTT AND J. LEE

As in most scientific investigations, research into the aetiology of malignant hyperthermia or malignant hyperpyrexia (MH) has itself been characterized by the oddities of the disorder. Until stressed, the affected organism or tissue is to all intents and purposes normal in structure, function and appearance, with few exceptions, thus complicating the elucidation of mechanism, detection of affected individuals, and establishment of clinical studies. It is with good measure of hindsight (the expert's privilege) that we recount the major and continuing tasks of MH investigations: (1) to distinguish between primary and secondary roles in aetiology; (2) to discern which conditions are in part the result of acute MH and which are in part the result of an imbalance between supply of substrate and energy consumption.

During general anaesthesia control of body temperature is absent and temperature can therefore drift up or down. Because general anaesthetics result in at most a 10–15% decrease in whole body metabolism [108], heat production is not drastically reduced. Thus it is primarily cutaneous vasodilatation in a cool environment that is responsible for the passive cooling that tends to occur during anaesthesia. If whole body metabolism and hence heat production markedly increase, body temperature can precipitously increase.

HISTORICAL AETIOLOGY

When Denborough and Lovell first described MH in 1960 [26], they had little direct information concerning aetiology, but appropriately surmised that it was a pharmacogenetic disorder. Further case reports added descriptions of muscle rigidity [97, 107]. Because there were few actual data other than case reports, and because controlled collection of data was impossible, the questions were overwhelming. Was this a new observation? Denborough's original family traced anaesthetic-related deaths to 1922, presumably all associated with diethyl ether. Yet why wasn't a familial correlation identified and reported sooner? Why did the flood of ominous and frightening case reports only begin in the 60s? Did scepticism in regard to these anaesthesia deaths discourage early reporting and investigation? How much was the apparent increase in MH episodes related to newer anaesthetic agents or techniques? Did the lack of sympathetic stimulation of the new volatile agent halothane upset a necessary balance that ordinarily helped to control muscle metabolism or thermoregulatory balance during anaesthetic stresses? Did the sympathetic stimulation of cyclopropane and ether "tend to prevent" full-blown episodes? In the maturing field of anaesthesia, did the pressures of defining roles in the operating theatre delay the development of observations such as these into organized reports? Did muscle hypertonicity with its associated increase in heat production initiate the metabolic changes, and did the central nervous depression of anaesthesia contribute to it? These and other implied questions confounded observers then, and some of these continue to confound. The number of cases mounted, with a mortality rate of 75%. As Stephen [106] perceived it, some mechanism is set in motion that has "full sway" in the absence of effective thermoregulatory power.

Porcine research fortuitously focused in these same areas. Briskey in 1964 [6] described pale, soft, exudative (PSE) pork that could not initially be distinguished from normal muscle, but became obviously different after it was stressed at slaughter and underwent rapid postmortem change. This finding underscores the difficulties of MH research. Hall and colleagues in 1966 [58] described porcine MH in conjunction with rigidity during suxamethonium–halothane anaesthesia in three littermate swine, and correlated the response with human MH. Topel and colleagues [109] in 1968 confirmed that the porcine stress syndrome

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Gerald A. Gronert, m.d.; John Mott, m.d.; John Lee, ph.d., m.d.; Department of Anesthesiology, University of California, Davis TB 170, Davis, CA 95616, U.S.A.

(PSS) was a disorder of muscle. It was obvious that PSE pork was a product of PSS swine that were unduly stressed. In 1969 Harrison and others [61] demonstrated that the muscle ATP depletion test could identify affected pigs. In 1970, Berman and colleagues [5] described the clinical, metabolic and biochemical course of MH in the susceptible pig and further underscored the importance of the pig as an animal model. They clearly demonstrated that metabolic changes occurred first, and that other changes were compensatory. Britt and Kalow in 1970 [11] could exclude central nervous system causes and could incriminate muscle, but they nonetheless described the disorder as "Aetiology Unknown".

New findings pinpointed skeletal muscle as the major aetiological factor in acute episodes of MH and demonstrated an association with myopathies. Blood concentrations of creatine phosphokinase correlated at least in part with susceptibility, in non-triggered patients as well as during acute episodes [24,67]. Contracture-producing drugs, well known to muscle physiologists, produced lower threshold responses in muscle from susceptible patients [70]. Procaine and lignocaine, perhaps because of effects upon muscle, were noted to be effective in treating clinical episodes [70,71], although lignocaine was later temporarily condemned on theoretical grounds because of its *in vitro* action in releasing calcium from sarcoplasmic reticulum [8] (see SR: drugs in MH). Suxamethonium could produce violent fasciculations and rigidity. Muscle rigidity (even without the use of suxamethonium) frequently developed during acute MH, but was not a terminal event. Observations in patients undergoing limb surgery with use of a tourniquet confirmed that MH arises in muscle, and that the muscle must be perfused for MH to develop. These patients developed MH involving whole body rigidity while the tourniquet-isolated limb remained flaccid [29,98].

Various theories emerged and diverged. These included loss of control of calcium ion within the muscle cell, myotonia, failing cell membrane function, insufficient ATP, decreased muscle phosphorylase with inadequate ATP production [10,11] and uncoupling of oxidative phosphorylation [116]. This last theory was discounted by the theoretical arguments of Wang, Moffitt and Rosevear [111], who calculated that uncoupling alone would not account for the increased heat production; they did note that muscle contractile activity could result in the requisite amount of heat production.

1971 marked the First International Symposium on MH [41]. This conference summarized findings to date and detailed normal and proposed abnormal physiology. The theory of altered calcium transport within the cell was generally accepted. MH was more or less defined as a genetically determined membrane defect involving the sarcoplasmic reticulum (SR), perhaps at the triad (transverse tubule–SR junction). Other aetiological considerations included inhibition of monoamine oxidase, with a reversal of the trend toward hypothermia usually observed during anaesthesia. The sudden onset of MH suggested a superficial membrane phenomenon rather than a direct effect upon mitochondria. Studies using dinitrophenol implied an alteration in oxygen utilization and a possible toxic effect of increased oxygen tension [39]. However, the contracture related to dinitrophenol was not typical of MH contractures and the number of pigs in the oxygen studies was not sufficient to provide adequate data for definitive conclusions. These proposals were not confirmed by others.

After the First Symposium, theories concerning aetiology included all membranes and tissues of the body, in part because of the involvement of calcium ion in the reactions of virtually every cell in the body [8,9]. Examination of function of intracellular organelles, SR and mitochondria, began to uncover modest alterations in basic functions. Muscle biopsy was becoming accepted as a diagnostic tool; it further demonstrated that muscle was abnormal at the level of the basic regulatory mechanisms of muscle contraction: various contracture-producing drugs, regardless of their mode of action, induced a contracture in susceptible muscle at a threshold lower than that of normal muscle, including the classic potassium contracture [84]. This in part led to the proposal that MH appeared to be an exaggeration of normal rather than different pathological responses [83].

In summary, MH appeared to be a subclinical primary myopathy with secondary systemic pathophysiology; the systemic consequences were marked because muscle comprises about 40% of body mass.

CENTRAL NERVOUS SYSTEM

Control of thermoregulation is not disturbed in MH, but there may be a suggestion of CNS involvement. LaCour, Juul-Jensen and Reske-Nielsen [75] had reported a young boy who developed peculiar central nervous responses after receiving suxamethonium. It had been injected to a tourniquet-isolated limb; after the tourniquet was deflated, peculiar fasciculations occurred, followed by apnoea. This observation has never been satisfactorily explained. Kerr, Wingard and Gatz [73] demonstrated that extradural blockade could prevent the rigidity of halothane-induced MH in the blocked limbs of susceptible pigs. They did not measure metabolic responses, but observed muscle tone and temperature. Gronert, Milde and Theye [48] contradicted their findings and conclusions by demonstrating that the muscle paralysis of total spinal anaesthesia did not block the metabolic responses of MH that were induced by halothane, and that pigs could experience typical episodes of MH during blockade of afferent and efferent central nervous system responses. Britt and colleagues [12], using the technique of motor unit counting in humans, inferred CNS dysfunction. However, the results of the test denote a non-specific myopathy, not necessarily a motor nerve problem, and interpretation of the results may be controversial. Lack of involvement of the CNS was shown by the observations of Artru and Gronert [3]: metabolism of the brain during porcine MH was not primarily abnormal and effects upon it and energy stores were secondary to the temperature, electrolyte, acid–base and cardiovascular disturbances of an acute MH episode.

SYMPATHETIC NERVOUS SYSTEM

Earlier, and now, the major emphases and disagreements concerning the role of the nervous system in MH involve the sympathetic portion of the autonomic nervous system. Wingard [118], at the Wausau symposium in 1974, proposed his theory of stress as a major precipitant in human MH. Susceptible families that he was following had an apparently increased incidence of sudden unexplained deaths, as a result of heart attacks, motor car accidents, etc. Moulds [83] believed that some effect of catecholamines might stimulate MH responses. Britt correlated MH susceptibility in humans with abnormal myocardium (*vide infra*: MYOCARDIUM) and with abnormal responses to sympathetic agonists as inferred from increased morbidity and mortality following their use; she summarized others' findings as suggesting an exaggeration of catecholamine innervation with multiple indirect effects on myoplasmic calcium [8, 9]. Campbell's group [16, 17] examined sympathetic responses in susceptible unanaesthetized humans under tightly controlled conditions, via measurements of heat production, temperature and blood hormone–metabolite concentrations. There were subtle, but not outstanding, indications that variations in heat dissipation might imply sympathetic dysfunction in susceptible subjects. However, the changes were not marked, and they sometimes were opposite to what one would anticipate—that is susceptible patients, in direct contrast to normal patients, showed a complete absence of exercise-related dietary-induced thermogenesis. It may be more difficult to demonstrate sympathetic dysfunction in the susceptible human, if it is indeed present, because of ethical limitations restricting the degree of stress in a species that is not as genetically pure (and therefore probably not as susceptible) as the inbred susceptible pig.

In the pig model, Williams and colleagues developed an extensive theory incriminating noradrenaline as the major factor in MH, both as a basic abnormality and as a trigger. This theory has not particularly changed over the years [113, 114]: they believe that the susceptible pig has a continually increased metabolism as a result of excessive noradrenaline effects upon its abnormal MH-affected muscle. The pig constantly releases or controls the extra heat and acid by its relatively limited homeostatic mechanisms (swine are unable to sweat). When some factor, such as a hot environment, exercise, fighting, coitus or general anaesthesia suddenly stresses the animal, it cannot control this additional heat production and MH erupts, very much like steam through a pressure control valve. Against Williams' theory are several observations. The susceptible pig is usually genetically pure and easily triggered by environmental factors; measurement of increased metabolism in a chamber, for example, does not relate to the basal state in the unsedated pig, an observation made by Williams himself [115, 116]. Further, others have not observed increased basal metabolism in the sedated pig [49, 79].

During anaesthesia, the sympathetic nervous system does not have a primary role in porcine MH, for acute sympathetic denervation secondary to total spinal anaesthesia completely prevents the usual increases in circulating catecholamines without altering the MH episode itself [48]. Finally, Williams [113, 114] suggested that the extreme increases in blood concentrations of catecholamines, especially noradrenaline, are further support for his theory. Several authors, however, have not observed triggering in susceptible pigs given infusions of noradrenaline, based in part upon lack of change of temperature [57, 61]. Further, Gronert and White (unpublished observations) have used noradrenaline infusions during nitrous oxide–barbiturate anaesthesia to increase blood concentrations to 145 ng ml^{-1},—considerably greater than those generally seen in acute MH, with no evidence for triggering, based upon observation of aerobic metabolism and glycolysis. At the end of the noradrenaline experiment, these pigs were triggered by halothane and suxamethonium.

Lucke, Hall and Lister have favoured a sympathetic mechanism for MH, at least in part. They observed that α-agonists could initiate MH episodes [55], and that α- and β-antagonists could modify these episodes [76]. α-Antagonists did not block initial muscle responses, but altered temperature and arterial pressure phenomena. β-Antagonists modified glycolytic and acid–base changes, but all swine died—that is, mortality was unaffected.

These studies and their modifications are difficult to interpret, because of differences from typical episodes and because of difficulties in preparing stable animal models with various operative and drug-induced situations. As an example, in acute porcine MH episodes initiated by phenylephrine, the increase in temperature preceded the increase in lactate concentration [55], whereas when halothane initiated MH, the increase in lactate concentration preceded the temperature increase [49, 79]. This suggests that phenylephrine may have produced environmental triggering as a result of decreased heat loss or ischaemia secondary to vasoconstriction (known triggers of MH or PSS responses), rather than by the direct effect of this α-agonist. In addition, in this same study, noradrenaline increased temperature, but by approximately the same amount in normal and susceptible pigs, a finding confirmed by Gronert and White (unpublished observations). Another study by Lucke and colleagues [78] involved bilateral adrenalectomy and use of adjuvant sympathetic blockers. However, the fitness of these swine following preparation was open to question: of 10 adrenalectomized pigs, six survived for inclusion in the procedure; after the study, it was not possible to extubate the tracheae and four of six died of ventilatory difficulties within 2 h of the end of the experiment. The lack of triggering in these swine is therefore subject to interpretation—was this protection and blocking, or was it borderline survival?

We should note that porcine MH is different from human MH; in the absence of exposure to anaesthetic agents, porcine awake episodes that are identical to classic anaesthetic MH episodes can be predictably initiated with any sort of stress. This is empirical support for any theory involving the sympathetic nervous system. Gronert, Milde and Taylor [46] examined this aspect in the absence of anaesthetic effects, using a mutilating preparation in which one could measure metabolism in the absence of nervous, hormonal or autonomic influences. In this preparation, the pig underwent corporal section at the level of the first lumbar vertebra, with perfusion of the caudal third of the body by a pump oxygenator–heat exchanger. Sympathetic agonists of the α variety (phenylephrine) or β variety (isoproterenol) did not trigger hypermetabolic responses; interestingly enough, the only effective triggers in these experiments were carbachol (depolarization) and increased temperature.

The authors' overall view is that the role of the sympathetic nervous system in MH is secondary. It is certainly an important part of any MH episode; however, the reaction starts in skeletal muscle and the homeostatic reactions to such a severe response aid in maintaining survival, much as with any other severe stress. α- and β-antagonists modify these episodes in the experimental situation, but without consistently and completely preventing or ameliorating them and, in the case of β-antagonists, without reducing mortality. Central sympathetic findings are variable: Wheatley and colleagues [112] did not find abnormalities in porcine central nervous system bioamines, while Draper and colleagues [28] observed lower concentrations of dopamine in the caudate nucleus of susceptible pigs. They interpreted this as a disturbance of the dopaminergic system of the basal ganglia, with no dysfunction of adrenaline or noradrenaline metabolism. The serotonin inhibitor ketanserin has altered the course of porcine MH in an inconsistent manner [90]. Consistent and reproducible beneficial effects of *any* drug therapy were not seen until Harrison

[59] reported the use of dantrolene. Initiation of MH episodes appears to relate less to sympathetic activation than to depolarization (see MUSCLE: *Sarcolemma* and *Depolarization*), although both factors could be involved.

MYOCARDIUM

Britt [7] wrote an editorial in the *New England Journal of Medicine* that introduced and explained MH as a general medical problem. She referred to MH as a disease of skeletal and cardiac muscle, but she did not describe any specific abnormalities of cardiac muscle *per se*. This editorial apparently reflected her bias about cardiac muscle and her presumptions that she believed would be confirmed as more data were accumulated. However, supportive evidence is weak. Wingard [118] believed that myocardial problems, either primary, or secondary to sympathetic overactivity, resulted in sudden death, either as a result of "heart attacks" or from a higher incidence of events such as automobile accidents than were seen in the general public. Huckell and colleagues [65] reported life threatening arrhythmias in four susceptible humans, two of whom had a family history of sudden death; these patients had not had awake pyrexic crises. The authors concluded that there may be a unifying concept for various manifestations of MH; that is, there may be abnormal calcium release in the heart also. Huckell and colleagues [64] reported that 26 of 93 patients identified as positive by biopsy (mean age 32–34 yr), had ECG conduction defects, repolarization abnormalities or increased voltage suggestive of hypertrophy. They did not compare the incidence of these findings with that in a control group of normal patients. These authors continued their studies with a series of catheter-guided human myocardial biopsies [80]; these biopsies did not demonstrate MH-related defects, but did show changes consistent with known artefacts of heart muscle following excision, preservation and sectioning. Kawamoto and colleagues [72] demonstrated normal cardiac perfusion in a patient convalescing from an acute MH episode.

The question remains, does the heart have a functional defect which is not detectable structurally, or do these findings signify that the heart is normal? Others have reported changes in myocardium of susceptible pigs. Hartigan and McLoughlin [62] reported ostium primum lesions in a litter of susceptible pigs. Roewer and colleagues [95] measured abnormal excitation–contraction coupling after halothane was administered to isolated heart muscle from susceptible pigs. However, the physiological right heart bypass studies of Gronert and colleagues [50] demonstrated normal sympathetic reflex responses to stress: during whole body MH initiated by halothane and suxamethonium, the sympathetic nervous system produced, via β-agonist effects, major changes in cardiac metabolism. Cardiac oxygen consumption increased five-fold and efficiency decreased about eight-fold, but the responses were completely blocked by huge doses of propranolol (40 $\mu g\ kg^{-1}\ min^{-1}$ by continuous i.v. infusion). There were no suggestions of MH triggering in the heart: neither lactate nor potassium was released during acute MH episodes in the absence of treatment with propranolol. These responses imply secondary sympathetic effects which then altered myocardial physiology.

Britt [9] has inferred from clinical evidence that cardiac muscle is abnormal and that cardio-active drugs may be harmful in MH. She has developed this position in part because of her unparalleled MH file of human case reports. Her statistical analysis indicates a direct relationship between use of drugs such as digoxin, calcium and adrenaline and increased mortality. She concludes that these drugs can produce MH responses in skeletal and cardiac muscle and that, in the presence of these drugs, the heart may not function adequately for recovery. However, association does not imply cause. We believe that critically ill patients were given more of these supportive drugs and that it is consequently difficult to associate increased mortality with one specific facet of treatment when there are multiple life-threatening factors involved in MH episodes. Gronert and colleagues [43], using a right heart bypass preparation, tested this hypothesis concerning the response to cardiac drugs. This study was relevant to care of humans because the pig is more closely inbred and because there is greater control of genetic factors; therefore drug-related risks should be more obvious in the pig model. Calcium, digoxin and potassium were not dangerous drugs in regard to their effects upon cardiac muscle. All stimulated cardiac metabolism in both normal and susceptible pigs, but none precipitated abnormal responses.

OTHER TISSUES

The foremost and single confirmed representative of a weak list of other tissues and organs which could be primarily involved in MH is porcine red blood cell fragility [63], but not human red cell fragility [40]. While disseminated intravascular coagulation occurs in acute MH episodes, this is not likely to be an example of involvement of other tissues. It is rather more likely to be the result of release of tissue thromboplastins as a result of increased cellular permeability or cell breakdown secondary to the stresses of acidosis, increased temperature and ion fluxes. Platelets have been proposed as being primarily involved in MH because of the presence of a contractile apparatus similar to that of muscle; this has led to the development of a diagnostic test based upon platelet ATP depletion by halothane; this test has not been confirmed by others in numerous studies and the inescapable conclusion is that MH does not directly affect platelets in a way that we can presently measure [13]. A recent abstract re-introduced the concept of platelet abnormalities via a modification of the earlier studies, using platelet ATP depletion in conjunction with electron microscopy [103]. It is premature to conclude that this modification establishes primary platelet dysfunction. Porcine platelet monoamine oxidase activity is not different from that in normal swine [22]. Several articles had suggested that plasma cholinesterase function was deficient in some susceptible families. Subsequent investigation did not confirm this proposal and the consensus is that these families were not representative of MH susceptible families in general [51]. Increases in hepatic temperature that occurred early in porcine MH episodes had been interpreted as primary involvement [5]. Data from Darrah and colleagues [23] on the function of isolated liver slices from susceptible pigs supported this position. However, direct examination of hepatic metabolism did not confirm these inferences, suggesting that the liver is not abnormal in MH susceptible individuals [14, 44, 56]. While calcium is a ubiquitous ion serving as a second messenger or mediator in almost all tissues, and the presumption of a generalized abnormality is therefore attractive, the evidence supporting or confirming such a role is not at hand. Klip and colleagues [74] described abnormal MH-related calcium fluxes in lymphocytes that were isolated from susceptible pigs and humans and exposed to halothane. Again, we need confirmation—perhaps this will be the breakthrough in regard to abnormalities of other tissues. Direct and consistent support is virtually non-existent for theories involving other tissues and organs.

It appears, and perhaps quite logically, that the genetic selection used to develop porcine skeletal muscle to an extreme has led to abnormal skeletal muscle responses to stress and, since other tissues and organs were not similarly selected, there is no reason to expect them to be abnormally involved in a consistent manner in regard to MH [43].

MUSCLE

General considerations

Skeletal muscle, then, is the principal aetiological focus. Physical responses to environmental stresses indicate that the muscle itself, in the absence of other factors, has exaggerated and magnified responses. This is exemplified by the effects of external heating. Intact susceptible pigs exposed to a warm environment have increased stress responses in muscle after slaughter [6]. They also are triggered into MH reactions by heat alone [91]. That this is a direct muscle response independent of sympathetic, hormonal or reflex activity is shown by the response of an isolated perfused caudal preparation [46]. Caudal muscle perfused, oxygenated and warmed by a heat exchanger and external heat lamps responded similarly as did the intact pigs of Ørding, Hald and Sjontoft [91]: at temperatures greater than 40–41 °C, oxygen consumption and lactate production of muscle from susceptible pigs precipitously increased, an effect not observed in muscle from normal pigs that were equally heated. Heat production during porcine MH episodes is accounted for by stimulation of aerobic metabolism, glycolysis, neutralization of hydrogen ion, hydrolysis of high energy phosphate esters and ion pumping [5, 52]. The increase in whole body oxygen consumption in the intact animal is accounted for by increases in muscle metabolism [44]. It had been proposed earlier that futile cycling of certain metabolic reactions might explain the runaway metabolism of MH [20]. Futile cycling is important in the bumblebee, as the thoracic flight muscles must be warmed to 30–32 °C to be active enough to sustain flight. It consists of cyclical increased metabolic activity unrelated to specific functions or reactions other than those of increasing heat production, until the muscles have been sufficiently warmed. The accelerated substrate cycling of glycolysis in MH does not appear to be futile; it is apparently related to a need for additional ATP for calcium pumps, particularly at a time when mitochondrial function may be limited. This is in keeping with recent findings that support the theory of altered calcium control (see MUSCLE: *Mitochondria, Sarcoplasmic reticulum*). Studies evaluating the triggering action of calcium, digoxin, potassium and hypercarbia in susceptible pigs demonstrated that potassium was the only factor that would trigger MH responses in skeletal muscle [43]. This effect of potassium is analogous to its actions *in vitro* [84]. These findings confirm the supposition that calcium will not trigger skeletal muscle, because the gradient from extracellular fluid is huge, at least 10^3, and because exogenous calcium, even in large doses, would alter that gradient very little. In the cited study, ionized calcium concentrations reached 7.5 mmol litre^{-1}. Hypercarbia, to 21.3 kPa, with its associated respiratory acidosis and sympathetic stimulation, and digoxin at extreme toxic concentrations (50 ng ml^{-1}) were also ineffective in triggering susceptible skeletal muscle. Because of the cardiac toxicity of these drugs when given in high doses, these animals were perfused via cardiac bypass, an advantage which eliminated cardiac depression or toxicity as a factor in evaluating results [43].

Rigid v. *non-rigid muscle*

Britt and Kalow [10,70] divided MH into rigid and non-rigid classifications, based upon their analysis of case reports; rigid patients had the classic MH symptomatology of acidosis, fever, tachycardia, etc., while non-rigid patients had few confirmatory signs. These classifications did not survive rigorous examination [42]. The use of 37 °C rather than room temperature muscle baths at Toronto led to the demise of this theory. The increase in temperature diminished the number of higher-than-normal threshold responses (which had been associated with non-rigid patients). The present view suggests that rigidity depends primarily upon the intracellular concentration of free unbound ionized calcium; if this approaches 5×10^{-5} mol litre^{-1}, or if mechanical threshold is altered, rigidity is likely [8,42].

Sarcolemma

The sarcolemma (surface membrane and transverse tubules) responds to stimuli abnormally. It is difficult to discern whether the abnormality rests with the membrane itself or whether the defect lies with internal sarcoplasmic structures which respond to the transferred signal. These abnormalities are characterized by the following. There is a lower mechanical threshold in susceptible muscle membrane; that is, a lesser degree of depolarization produces a contracture [15,38]. Halothane depolarizes the surface membrane [37] and various methods of electrical stimulation result in exaggerated responses [1,43,93,94]. Because the halothane depolarization of about 7–15 mV develops after 20–30 min exposure, the mechanism could be related to metabolic changes within the fibre proper rather than to a direct membrane effect [37]. Data from multiple pulse stimulation, one to six pulses with a 5-ms interval between each, support the theory of abnormal calcium transients and abnormal excitation–contraction coupling [93]. Each 5-ms pulse basically releases a "pulse" of calcium that activates the contractile mechanism; susceptible muscle responds with a faster rate of increase in, as well as greater, tension. Because of overlap of data, these differences were not dramatic, although mean values differed significantly. The use of dantrolene markedly enhanced these differences and eliminated the overlap of data. Dantrolene inhibits the response of both normal and susceptible muscle, so that both have a lower tension and a slower rate of increase in tension. Presumably the susceptible muscle defect permitted greater release of calcium with multiple pulse stimulation. Therefore the susceptible muscle recovered a significant portion of its responses at a time when the normal muscle was still depressed by dantrolene. These data suggest that depolarization *per se*, if exaggerated, may be a factor in the aetiology of MH episodes. Steiss, Bowen and Williams [105] noted increased amplitude and duration of motor unit action potentials in susceptible pigs; these findings may further support the theory of increased calcium release with motor nerve stimulation. Nelson, Flewellen and Arnett [87] observed that the onset of mechanical tension was delayed in susceptible pigs in comparison with normal pigs. However, their stimulation artefact obscured the onset of the muscle action potential, thus weakening their major observation of prolonged electromechanical delay.

Intracellular organelles

Specific intracellular muscle organelles include the mitochondrion and sarcoplasmic reticulum (SR). Both human and porcine preparations have been examined by isolation techniques in numerous reports over the past 17 years or so. The process of isolation may alter the function of intracellular organelles in ways that we do not realize, and we therefore may not be warranted in drawing conclusions based solely upon the response of these isolated fragments. Without presenting a review of the considerable detail and variability of all these studies, the consensus can be said to be that these studies demonstrate changes consistent with a myopathy, that they are non-specific changes, that they are of insufficient magnitude to account for MH, and that they do not define a unique defect attributable to MH.

Mitochondria

Cheah [19] has proposed, and Fletcher and Rosenberg [32] support, a theory that mitochondrial phospholipase A2 is abnormal and that this enzyme causes release of fatty acids which acutely inhibit the function of SR. This in turn causes the characteristic overt malfunctions of MH. The release of phospholipase A2, however, is dependent in part upon release of calcium, which stimulates this entire process. Since MH is thought to be a disorder of calcium metabolism or of calcium transients, it is difficult to determine which is the primary alteration, calcium or phospholipase. The response therefore could be a secondary characteristic of MH; at present this fascinating theory is not confirmed. Could the phospholipase A2 response be a reflection of typical and usual biochemical responses that occur in susceptible cells or organelles that do not tolerate stress? Is this perhaps the result of an imbalance between energy supply and demand because of the limited ability of mitochondria to supply ATP when they are binding overflow amounts of calcium? Stadhouders and colleagues [104] have elegantly demonstrated by electron microscopy–microprobe analysis that mitochondria participate in reserve compensatory responses involved in porcine MH. During acute MH episodes, mitochondria actively sequester calcium ion, an action reversed by treatment with dantrolene. The implication is that mitochondrial function is restricted and limited by the forced compensatory uptake of calcium [27]. This may therefore explain why whole body oxygen consumption does not increase as much during acute MH as one would expect; for example, as much as it does during exercise. This limited increase in whole body oxygen consumption could also be the result of a limited involvement of whole body skeletal muscle—not all muscles might be participating in an MH reaction.

Sarcoplasmic reticulum

SR is the focus of the current theories of malfunction during MH episodes. The clinical course and laboratory data strongly suggest that SR no longer can control intra-fibrillar concentrations of free ionized unbound calcium and that the associated hypermetabolism is a result of compensatory stimulation of calcium pumps. This is specifically supported by the delicate studies of Lopez and his colleagues [2, 77], who measured intracellular ionized calcium concentration using an ion-specific microelectrode (see also reference [104], *Mitochondria*). They observed increases at rest in humans (intact intercostal) and in pigs. They also saw dramatic increases in ionized calcium in intact pigs during acute MH with reversal of the increase by dantrolene. One aspect of these findings deserves comment. It is paradoxical to find increases in calcium ion at rest; there should be signs or findings related to this increase, in particular an increase in basal metabolism, such as that postulated by Williams [113]. This is not the case. It seems probable, in the absence of confirmatory data or of other supportive findings, that the increase in intracellular calcium ion noted at rest may be artefactual, perhaps caused by perturbation of the cells during measurement with the microelectrode. MH susceptible muscle cells may be unable to tolerate such stress, in contradistinction to the stability of normal cells. The alternative theory is that there has been a resetting of resting ionized calcium to a non-energy-demanding level that is perhaps dangerously close to one which could activate contractile activity.

Crucial to our understanding of MH is a knowledge of basic muscle physiology. At present, muscle physiologists do not yet understand the mechanism by which the wave of depolarization from the transverse tubule is transmitted to the SR or to its triad. Dantrolene acts in this same area of muscle; as a result, its specific action, probably closely related to the mechanism of MH, cannot be used to define the lesion of MH.

Two mechanisms of calcium release are postulated: depolarization-induced release as the likely putative mechanism for skeletal muscle, and calcium-induced release as that for cardiac muscle [50]. In the first, the action potential in the transverse tubule is transmitted to and depolarizes the terminal cisterna of the SR, thereby increasing permeability to calcium. In the second, an amount of calcium too small directly to cause contraction enters the fibre with depolarization and regenerates a much larger increase in calcium release by increasing the permeability of the SR. Both of these types of calcium release lead to contraction, and the additional free, unbound calcium ion is then taken up and bound by SR. Abnormal patterns of calcium-induced calcium release have been observed in samples of susceptible skeletal muscle. While there is not yet a "normal" skeletal muscle role for this alternate mechanism for calcium release, these studies [81, 89] suggest that calcium-induced calcium release may be a part of the abnormal response in MH muscle. For some as yet undefined reason, there may be a strong enhancement of calcium-induced calcium release in MH.

Calcium-induced calcium release may be relevant in MH only at a time when dysfunction is occurring, or, it may relate only to the abnormality of MH. One factor that has impeded application of this theory to MH is the lack of blocking action by dantrolene on isolated vesicles of SR [81]. This paradox has apparently been solved by Ohta and Endo [89], who determined that dantrolene would block this release at 37 °C but not at 22 °C (a frequently used temperature for these studies).

Drugs in MH. As an episode of MH progresses and the combination of acidosis, increased temperature and electrolyte imbalances leads to failure of cellular mechanisms, or loss of energy charge, cellular permeability increases and there is a beginning of breakdown of the organism. *Dantrolene* appears to be specific for treatment, because it rapidly reverses these changes under a variety of experimental and clinical conditions. It is not directly diagnostic of MH, because it can aid in controlling high temperature or muscle rigidity regardless of cause. For example, it reduces excessive normal muscle function, heat production and energy consumption when altered by fever. *Calcium antagonists* are not effective in treating MH, based upon controlled swine studies [36], despite supportive evidence for a therapeutic effect in humans *in vitro* [68] and *in vivo* [21], and in pigs [66]. In the last study, diltiazem was used for *in vivo* treatment in pigs, but there were two instances of complete heart block. These drugs act on surface membrane calcium functions rather than upon SR, and therefore seem less likely to alter, safely and effectively, the calcium fluxes involved in MH reactions. *Procaine* and *lignocaine* have historically been associated with aetiology. Procaine prevents the caffeine contracture of isolated muscle by reducing SR calcium efflux (although it is ineffective once the contracture is established), and lignocaine induces or worsens contractures because it increases efflux from the SR. These effects require millimolar concentrations of these drugs, far greater than the plasma values achieved in clinical usage. However, because of these theoretical considerations, procaine was proposed as a therapeutic drug for MH, and lignocaine was condemned as dangerous for susceptible patients. In time these opinions changed. Porcine studies demonstrated the lack of therapeutic efficacy of procaine [47, 86], and human–porcine studies demonstrated the lack of danger of lignocaine [4, 60, 119].

To summarize this information about the SR. MH appears to be the result of an overall malfunction of the SR; the location of the lesion, or combination of lesions, is somewhere beyond the endplate and somewhere before the contractile mechanism. The location may be primarily at the transverse tubule–SR junction; it may be a functional lesion that simply alters excitation–contraction coupling [87, 93]. As stated above, the role of the sympathetic nervous system appears secondary, but we cannot ignore the fact that catecholamines have important synergistic effects upon the actions of skeletal muscle, such as strengthening of contraction and acceleration of the rate of contraction, that may support and augment MH responses.

Depolarization

It is the senior author's belief that depolarization may be significant in MH reactions, whether these are anaesthetic-induced or "awake" (see *Sarcolemma*). (1) Halothane depolarizes skeletal muscle membranes. (2) The mechanical threshold of susceptible muscle is lower than that of normal muscle and therefore predisposes to easier development of a contracture. (3) Halothane decreases the mechanical threshold of muscle. (4) Suxamethonium and carbachol depolarize normal and susceptible muscle, and both trigger susceptible but not normal muscle. (5) Electrical stimulation triggers susceptible but not normal muscle. (6) Non-depolarizing neuromuscular blocking drugs delay MH episodes. Evidence against this theory is the action of 4-aminopyridine, which increases acetylcholine release at the endplate, but does not trigger hypermetabolism in susceptible swine [53]. It appears that extreme muscle activity or tension, either in the awake susceptible subject or in the susceptible individual who has increased muscle tension induced by drugs during anaesthesia, is predisposed to have an exaggerated stimulation of metabolism.

Rhabdomyolysis

Rhabdomyolysis may occur as a disorder by itself, related to exercise, certain stimulating drugs, or suxamethonium; it may, but need not, occur as part of an MH episode. Free myoglobin, the *sine qua non* of rhabdomyolysis, begins to increase in plasma soon after exposure to the causative stress, and several hours before creatine phosphokinase begins to increase [33]. It can be detected in the blood or urine almost immediately. It is cleared quickly, so quickly that in less severe instances the clinician may miss the increase, and think that the episode did not involve muscle breakdown.

TRIGGERING

Kalow, Britt and Chan [69] have suggested that an MH episode depends upon three factors: (1) an inherited predisposition; (2) internal and external qualifying factors that establish or protect from vulnerability; (3) the presence of triggering agents or conditions. The term "triggering" is apropos because the reaction is self-sustaining once started. Obviously, a greater influence by any of these individual factors may increase the likelihood of an episode.

Many believe that prior exercise may predispose susceptible individuals to more severe MH episodes if they are anaesthetized immediately afterwards; for example following exercise-related trauma. Briskey [6] and Van den Hende and colleagues [110] reported this phenomenon in swine. The aetiology of this accentuation is not certain; it may result from prolonged increases in intracellular ionized calcium concentrations secondary to multiple depolarizations, a position supported by the attenuating actions of non-depolarizing relaxants in MH [45, 54]. It might in part be related to the increase in temperature that occurs with sustained exercise. Others would suggest that sympathetic stimulation has prolonged effects that could account for this accentuation. A combination of all three may be responsible; based upon physiological mechanisms, this is possible and perhaps likely.

ASSOCIATED DISORDERS

While an MH susceptible subject is usually normal in regard to history, physical examination and appearance, (there are no obvious signs of the subclinical myopathy), there are some clinical disorders with obvious clinical abnormalities, some of which may be related to MH and some mere speculation. These disorders include myotonia, Duchenne's muscular dystrophy, central core disease, sudden infant death syndrome (SIDS), neuroleptic malignant syndrome (NMS) and heat stroke. Myotonia involves rigidity with suxamethonium, similar to the response of sustained conscious effort in myotonic individuals. Inbred myotonic goats develop this same rigidity to suxamethonium, but do not develop MH, even when the anaesthetic includes halothane [88]. Duchenne's is now recognized to involve MH-susceptibility [96]; it has always been known to involve an increased risk for anaesthesia: myocardial involvement, with difficult-to-resuscitate cardiac arrest; acute rhabdomyolysis of skeletal muscle, sometimes in the absence of signs of MH or identifiable changes in metabolism [100]. Central core disease, a clinical disabling myopathy that histologically includes multi-section loss of mitochondria ("central cores") definitely includes susceptibility, confirmed by reported episodes [34]. SIDS, or cot deaths, statistically correlates with MH [92] and has an increased incidence of positive muscle biopsies, but from only one laboratory [25]. This suggested association requires further analysis for, when directly observed, SIDS does not present as hypermetabolism, but as cessation of breathing during quiet sleep. Furthermore, statistical association can be misleading, for SIDS also correlates with administration of oestrogens to pre-term mothers [31]. Because MH susceptible muscle is more easily triggered into hypermetabolic responses by physical stimuli such as heat, we should expect more cases of NMS and heat stroke to occur in susceptible people—a position supported by the positive muscle contracture data of Caroff and colleagues [18]. However, the present authors believe that NMS occurs predominantly because of the central action of the psychotropic drugs; it may later trigger skeletal muscle (if susceptible) because of the varied temperature, electrolyte and acid–base abnormalities. This is an unsettled area.

ACQUIRED SUSCEPTIBILITY

Is there an aetiological explanation for acquiring susceptibility to MH? That is to say, can MH episodes be induced in non-susceptible individuals? The number of MH episodes reported in patients with various lymphomas almost suggests that there could be a predisposing effect [102]. There are several avenues of speculation, although none is necessarily directly related to lymphomas. Because general anaesthetics non-specifically perturb membranes [82] and because MH may be an exaggeration of normal responses [83], there is the possibility that prolonged exposure to MH triggering agents could eventually or ultimately disturb membrane homeostasis to the degree that MH occurs. One case report [85], in which approximately 26 h of anaesthesia was administered in a 36-h period, may exemplify this. MH involves a diminution in mechanical threshold, a situation in which contractile activation occurs more easily than usual; that is, a lesser degree of depolarization produces a contracture. Thus, a combination of drugs or factors (pore-formers, potentiators) can produce a decrease in mechanical threshold or an increase in permeability to calcium ion. If there is also concomitant depolarization of muscle membranes, there could be massive compensatory hypermetabolism, or an MH-type attack or episode. This perhaps is similar to the situation involving heat stroke, NMS, etc. With a certain amount of thermal insult alone in normal muscle, intracellular control of calcium can be lost [35] and, again, an MH episode could occur secondarily. If a number of the above alterations occurred simultaneously, in conjunction with exercise, increased activity or use of stimulant drugs, or both, MH susceptibility could well occur. Its presence might not be recognized unless the patient happened to receive a triggering anaesthetic.

ENERGY IMBALANCE

Whatever the mechanism or originating stimuli, an MH episode *per se* represents an *imbalance between energy supply and energy demand*. The pathophysiological picture of an acute MH episode is identical to that of *ischaemia*, as described in the brain [101], heart or other tissues or organs. The resulting changes have been well described, and involve scavenging of free radicals, action of quenchers or anti-oxidants, or reducing agents such as glutathione. These interactions could also be responsible for abnormal activity of adenylate cyclase, adenylate kinase, cyclic AMP and other enzymes under a variety of circumstances. The similarities are not complete, for calcium antagonists are not effective in treating MH (*vide supra, Drugs in MH*). Data are contradictory regarding the role of glutathione in MH—some positive [99] and some negative [30]. Again, even if abnormal activity is confirmed, the continuing difficulty is to decide which responses are primary and which are secondary. Primary dysfunction would occur in enzymes or membranes directly altered by susceptibility to MH, but normal tissues would be stimulated into typical and usual stress responses that occur secondary to abnormal stress responses elsewhere in the body or the cell. Susceptible skeletal muscle is exquisitely sensitive to perturbations and the hypothesized primary abnormal response, an increase in intrafibrillar ionized calcium, would promote a variety of (normal) secondary, and in part compensatory, responses. Further, these secondary responses might be difficult to examine in a situation separate from MH—a normal cell would not react unusually until stress reactions occurred.

In particular, if ATP concentrations tend to decrease as intracellular calcium increases, there may be a loss of normal cell membrane ionic gradients. As the mitochondrion in its reserve capacity begins to accumulate the excess calcium, the enzyme phospholipase A2 may be activated, with a release of free fatty acids. The release of free fatty acids will either alter SR function or add to the inherent SR dysfunction of MH. Mitochondrial calcium binding restricts mitochondrial function, and increases in oxygen consumption may then be limited, exaggerating the energy imbalance. Continuing blood supply to the affected tissues may result in oxidation of the free fatty acids, with the formation of prostaglandins, thromboxane A2 and free radicals. All of these, along with their interactions, alter permeability and conductances of membranes. These multiple events, in conjunction with the hypermetabolism of MH, could cascade into a destructive mayhem. Glutathione and other substances may be inordinately activated to counter some of these reactions. Many of the foregoing may overlap or resemble some of the changes in MH that have been considered as mechanistic. This is likely because of the confusion created by analysis of conditions that are in part the result of acute MH and in part caused by the imbalance between supply of substrate and energy consumption. At times during an MH episode there are elements of both. It is up to the MH "detective" to solve the riddle.

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CLINICAL PRESENTATION OF MALIGNANT HYPERTHERMIA

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As is the case with many medical disorders, malignant hyperthermia (MH) was first described in its most obvious dramatic form. This occurred in 1961, when Denborough and Lovell reported what we later learned was MH, in a young Australian undergoing routine surgery [7]. Over the course of the ensuing quarter of a century, many variations of MH have been described and we are still learning of variants of this syndrome. Even now, there is debate and disagreement as to the presentation of MH in humans [16]. In this article I will discuss the classic presentation of MH and some of the many variants of the syndrome.

Although the clinical manifestations of MH may be a cause for debate, the underlying pathophysiology is clearer. The work of Lopez and colleagues [22] indicates that the hypermetabolism of MH is related to increased intracellular calcium ion concentration; the cause of the release of calcium into the cell is not understood.

MH can be thought of as a spectrum of disorders, ranging from the "classic" case to those with unusual presentations and mild symptomatology. It would be expected, therefore, that the mortality and morbidity from MH would vary, depending on how rapidly the syndrome is diagnosed and treatment begun, and also on the inherent variability of the syndrome itself. The mortality from the most fulminant forms of MH is believed to be 10–15% [26], whereas mortality from other variants may be considerably less.

Also of importance in the manifestation of MH is the effect of concomitant drug administration and environmental factors. For example, it is recognized that non-depolarizing neuromuscular blocking drugs [20] and barbiturates can delay the onset of MH in susceptible swine.

The acuity of MH also depends on the concentration of the anaesthetic used. Clinical symptoms and signs are less severe in animals receiving 1% halothane than in animals receiving higher concentrations of the anaesthetic [1].

Environmental factors may affect the progression of MH. For example, it has been shown that progression and manifestations are more dramatic after animals are exercised [2, 35]. Increased body temperatures as a result of either environmental factors or perhaps intercurrent infection, may also aggravate the progression of the disorder [15].

Age may also affect the manifestations of MH. It has repeatedly been shown that the incidence of MH is higher in the paediatric and in the young adult populations than in the middle age and older adult population [26].

CLASSIC MALIGNANT HYPERTHERMIA

Those patients having some combination of the following characteristics are "classic" examples of the syndrome:

(1) High body temperatures (greater than 41 °C).
(2) Marked skeletal muscle rigidity.
(3) Metabolic and respiratory acidosis, frequently with base deficit of greater than 10 mmol.
(4) Myocardial changes, usually manifested as arrhythmia.
(5) Marked hyperkalaemia.
(6) Muscle breakdown as manifest by gross increases in serum creatine kinase (CK) concentration to greater than 20000 iu litre^{-1}, together with myoglobinuria.
(7) Family history of MH.

A variety of other changes may occur, including hypercalcaemia and disseminated intravascular coagulopathy (DIC), which is a leading cause of death in fulminant MH [15].

Patients with fulminant MH may have a paradoxical response to suxamethonium. In susceptible swine, suxamethonium in conjunction with

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halothane invariably precipitates fulminant MH [18]. However, in humans, fulminant MH may occur despite a normal response to suxamethonium.

Laboratory evaluation of MH usually reveals significant lactic acidosis and increased oxygen consumption and carbon dioxide production.

Arterial $P\text{CO}_2$ does not always adequately reflect severity. In a recent study, Gronert and co-workers [17], showed that arterial $P\text{CO}_2$ was significantly less than venous $P\text{CO}_2$ and suggested that femoral venous blood-gases are more helpful in assessing the severity of the MH episode than are arterial blood-gases.

Fortunately, probably less than 10% of all cases of MH progress to the fulminant variety. Ørding's study [26] of MH in Denmark over the period 1978–1984 revealed that only 6.5% of cases of MH were fulminant.

Recrudescence is another characteristic. Fletcher and co-workers [12] have described a patient with MH in whom metabolic symptoms lasted for several days. In the management of fulminant MH, it may be necessary to continue dantrolene into the early postoperative period and to assess the level of muscle destruction by frequent determination of CK. (CK will peak at 12–24 h after the episode of muscle destruction.) Massive amounts of dantrolene may be necessary to manage patients with fulminant MH, up to and exceeding the recommended 10 mg kg^{-1}. If managed well, the outcome is successful and neurological deficits should not be expected.

Biopsied skeletal muscle will show the classic changes of halothane-induced contracture as well as caffeine contracture at caffeine 2 mmol litre^{-1} or less [30] (see Ørding in this issue, p. 287).

Masseter muscle rigidity with suxamethonium

Muscle rigidity affecting the jaw muscles, particularly after an intubating dose of suxamethonium, is probably the most common manifestation of MH [28], especially in children. A negative history is obtained and the child anaesthetized with halothane or similar inhalation agents by mask. Suxamethonium is then given and trismus noted. In some patients muscle rigidity affecting other muscle groups is recognized. This muscle rigidity may last for 1–3 min and will then usually resolve. If the anaesthetic is continued, MH may develop within minutes, or may take several hours to appear [10].

The clinical characteristics of patients who have had suxamethonium induced muscle rigidity are [8, 28]:

(1) Suxamethonium used for intubation.
(2) Although halothane is commonly used for induction of anaesthesia, cases have been reported with ultrashort acting barbiturates.
(3) Usually children aged between 4 and 15 yr are affected. Patients in their 20s and early 30s also exhibit masseter muscle rigidity.
(4) Temperature increases are generally not marked, nor are significant arrhythmias noted. The muscle rigidity lasts for approximately 2–3 min and has been termed a "myotonic" reaction to suxamethonium, since a similar response is seen in patients with myotonic disorders [8].
(5) A family history of MH is generally not found.

Several studies have shown that the coincidence of masseter rigidity with muscle biopsy proven MH is in the order of 50% [8, 13, 28].

Ørding [26] found that 1 in 12000 patients who receive general anaesthesia and suxamethonium experience masseter muscle rigidity. A provocative retrospective study of masseter rigidity was carried out at the Boston Children's Hospital [31]. Approximately 1% of all children who received halothane and suxamethonium developed masseter muscle rigidity. Two of the 15 patients who developed such masseter rigidity had received suxamethonium previously without apparent problems. Of the records surveyed, 46% of the children who had masseter muscle rigidity were between the ages of 8 and 10 yr, but only 11% of all children undergoing surgery were in this age group.

Our recent studies have also found that masseter muscle rigidity was more common in children. The average age of patients referred for biopsy who had experienced masseter rigidity was approximately 10 years of age. We found neither gender predisposition for masseter rigidity, nor that it was associated with any particular operative procedure. Neither muscle histology nor EMG studies were able to distinguish those patients who are MH positive by halothane–caffeine testing from those who are MH negative.

If dantrolene is not administered after the episode of masseter rigidity, increased serum CK concentration will occur, along with a transient episode of myoglobinuria. Therefore, vigorous hydration and diuresis should be assured in the early postoperative period. If the perioperative CK concentration is greater than 20000 (upper limit of normal 200 iu litre^{-1}), then the likelihood of the patient being susceptible on muscle biopsy is extremely high, if there is no concomitant myopathy. Six of the 21 patients who experienced masseter rigidity and had serum CK concentrations greater than 20000 iu litre^{-1} were MH positive by muscle biopsy. The chance of the patient being MH susceptible if the serum CK value was greater than 15000 was 88%, and 82% if the CK concentration was greater than 10000 iu litre^{-1} (in the absence of other myopathies). Although some have continued anaesthesia with non-triggering agents after an episode of masseter rigidity, this can only be condoned if dantrolene is readily available and end-tidal carbon dioxide monitoring is undertaken. In any event, patients who have experienced masseter rigidity should be evaluated by a neurologist and, if possible, by muscle biopsy, since, occasionally, an underlying myopathy will be found. All patients who have myoglobinuria after anaesthesia should have a diagnostic muscle biopsy performed.

Prompt recognition of masseter rigidity and discontinuation of the anaesthetic is usually not associated with further progression to fulminant MH. Dantrolene may prevent the increase in serum CK concentration and myoglobinuria after operation and should, therefore, be administered soon after the episode of masseter rigidity.

The differential diagnosis of masseter muscle rigidity is limited. Apart from an inadequate dose of suxamethonium or underlying dystrophia myotonica or myotonia congenita, MH must be considered. Myotonic states can usually be diagnosed by clinical history and EMG.

What, then, can be said of the patient who experiences masseter muscle rigidity and who is MH negative by muscle biopsy testing, but also has had a transient increase in CK concentration? The patient should be advised to avoid receiving suxamethonium. Since suxamethonium-induced masseter rigidity has not been reported to be inherited, we have chosen not to biopsy family members of patients who experienced masseter rigidity but are MH negative by halothane and caffeine contracture testing.

A special problem is the discordance in incidence of muscle masseter rigidity and the incidence of MH. Even if 50% of all patients experiencing muscle rigidity were MH susceptible according to the data of Schwartz and colleagues [31], the overall incidence of masseter rigidity in children would be 1 in 200 cases. Clearly fulminant MH is not that frequent. Perhaps the underlying propensity to developing MH is much commoner in the population than we have imagined, and age affects the manifestations of MH such that, as we grow older, the ease of triggering the syndrome decreases. Further studies on masseter muscle rigidity, both epidemiological and pharmacological, are essential in order to guide the clinical management of postoperative MH.

Uncommonly, MH may present in the recovery room. The patient usually has had a normal anaesthetic course but, after operation, develops tachycardia, fever and classic signs of MH. In our studies of postoperative fever, we have found that fewer than 20% of patients will be MH susceptible on muscle biopsy. These data, of course, are derived from a selective population referred to a biopsy centre for evaluation. This is an especially perplexing problem, since postoperative fevers are not uncommon. Again, the extent of the increase in temperature, the presence of increased concentrations of CK and lack of underlying infection, will be the indications for diagnostic muscle biopsy.

MALIGNANT HYPERTHERMIA AND MYOPATHIES

Several myopathies have been associated with MH. The most well established association is between *Central Core Disease* and MH [14]. Muscle rigidity as well as fulminant MH have been described in patients with this condition [10].

Another uncommon myopathy associated with MH is the *King Syndrome* [23]. The typical features are cryptorchidism, pectus carinatum, low set ears, webbed neck and the development of kyphoscoliosis at an early age. Only a few cases of King Syndrome have been reported in association with MH. The usual clinical manifestations are fever and tachycardia, and other symptoms and signs indistinguishable from classic MH.

Patients suffering from *Duchenne muscular dystrophy* frequently have a most unusual presentation of MH [29]. Typically, after an uneventful anaesthetic with a triggering agent such as halothane, with or without suxamethonium, the patient exhibits a ventricular arrhythmia and cardiac arrest occurs in the recovery room in association with marked hyperkalemia and significant acidosis [21]. If the patient has received suxamethonium, marked myoglobinuria may become manifest.

It has long been known that patients suffering from *osteogenesis imperfecta* will display increased temperature during operation [27]. Several cases of classic MH have been described in osteogenesis imperfecta patients. We have biopsied five individuals with osteogenesis imperfecta and only one has been MH susceptible.

A few cases of MH have been described with other disorders, but since these are single case reports, no picture of a typical presentation emerges. Among these disorders are myotonia congenita, Schwartz–Jampal Syndrome, and hyperkalaemic periodic paralysis. Arthrogryposis multiplex has occasionally been thought to be associated with MH, but a recent report has failed to show an association [3].

MALIGNANT HYPERTHERMIA OUTSIDE THE OPERATING ROOM

In some swine breeds, MH can occur in the absence of pharmacological trigger agents. Susceptible pigs will develop signs and symptoms of classic MH initiated by stress, fighting, and even during mating [25]. Fortunately, this is not the case in humans. Anecdotal reports of sudden death among suceptible patients have been looked upon with scepticism, since many of the circumstances surrounding the deaths, and the family pedigrees, have not been thoroughly described in scientific terms [36]. If MH susceptible patients are more prone to sudden death, this is extremely rare. A single documented case of *episodic fever* relieved by dantrolene in a biopsy-proven susceptible patient has, however, been described [19]. More recently, two patients who experienced environmentally induced heat prostration were MH susceptible on halothane and caffeine contracture testing [11]. However, there are insufficient data to indicate if all susceptible subjects have a greater likelihood of suffering heat related syndromes in extreme environmental temperatures.

Sudden Infant Death Syndrome (SIDS), is a disorder that probably has multiple aetiologies, including airway abnormalities, undiagnosed congenital lesions and metabolic defects [33]. Of 15 families in which there was a history of SIDS, five parents were MH susceptible on halothane contracture testing [6]. In an epidemiological study, Ellis and co-workers have not been able to confirm a higher coincidence of SIDS in MH suceptibles [9].

The *Neuroleptic Malignant Syndrome* (NMS), is a syndrome characterized by increased temperature, muscle rigidity, acidosis, and autonomic disturbances which respond to dantrolene therapy [4]. However, the time course of this syndrome is hours to days, in contrast to MH, in which it is minutes. NMS is triggered by such psychoactive agents as haloperidol and phenothiazines. Of seven patients we have biopsied who suffered clinical NMS, five showed contractures typical for MH on halothane challenge [5]. However, others have not found typical contracture changes in patients biopsied for NMS. Other differences between MH and NMS are striking. For example, the butyrophenone droperidol is not a trigger for MH, but haloperidol apparently is for NMS. Many believe that NMS results from pharmacological blockade of dopamine receptors. Indeed, the dopamine agonist, bromocriptine, is a useful adjunct in the therapy of NMS. Another difference is the absence of a reported case of NMS in an MH patient or *vice versa*. Some NMS patients have even received suxamethonium for electroshock therapy without problems. NMS, however, is of special significance because it is estimated that 1.5% of all patients receiving psychoactive drugs will experience this syndrome with an approximate 20% mortality rate [32]. Until further clarification is available, it is prudent to treat NMS patients as if they were MH susceptible.

CONDITIONS THAT MIMIC MALIGNANT HYPERTHERMIA

Since fever, tachycardia and tachypnoea are relatively non-specific signs and symptoms, it might be expected that a variety of conditions will mimic MH.

Tachycardia and temperature increase are changes seen regularly in patients with sepsis.

Not uncommonly, small children are thoroughly covered during anaesthesia and are given humidified gases in order to prevent heat loss. In some cases, this may lead to increased temperature because of failure to dissipate endogenous heat.

Perhaps the most common cause of tachycardia and tachypnoea during anaesthesia is stimulation during light planes of anaesthesia.

Thyrotoxicosis marked by temperature increase, tachycardia, and hypertension is often difficult to distinguish from MH [34].

As mentioned earlier, rigidity with suxamethonium is the hallmark of not only MH, but also myotonias [24].

Phaeochromocytoma has many clinical signs and symptoms similar to MH. Tachycardia, hypertension and even hyperthermia may occur during an acute episode of phaeochromocytoma.

A rather unusual cause of increased temperature, along with hyperactive muscle activity, tachycardia and death, is the inadvertent injection of water soluble radiological contrast agents to the cerebrospinal fluid.

Not infrequently, hypoxic brain damage leads to postoperative temperature instability and convulsions, which are often attributed to MH. Most typically, the intraoperative course is marked by tachycardia and then precipitous bradycardia in association with "dark blood" (classic signs of hypoxia, usually the result of the delivery of hypoxic mixtures of gases or misplacement of a tracheal tube). Following cardiopulmonary resuscitation, the patient fails to awaken. Within 2 h, increase in temperature, posturing and convulsions occur, along with mildly increased serum CK concentrations (1000–5000 iu $litre^{-1}$). The patient either remains in a vegetative state or is markedly brain damaged. The diagnosis of MH is thus invoked to explain the temperature increase as well as the apparent muscle rigidity. In reality, however, these changes are the result of central nervous system damage, particularly affecting the hypothalamus.

CONCLUSION

Classic MH is the most dramatic and deadly manifestation of a syndrome that has many variants of presentation. Our current problem is to explain scientifically these variant presentations. They may all result from the same basic underlying pathophysiology, or may arise from several different intracellular derangements, all resulting in a final common pathway of increased intracellular ionic calcium and hypermetabolism.

Crucial signs that should alert the anaesthetist first to diagnose and then to treat MH are:

(1) Muscle rigidity after suxamethonium.

(2) Precipitous increase in end-tidal carbon dioxide concentration in the absence of a change in minute ventilation.

(3) Unexplained hypertension and tachycardia, especially with deep planes of anaesthesia.

(4) Unexplained myoglobinuria in the postoperative period.

(5) Unexplained marked increase in body temperature in the perioperative period.

It is apparent that, with the widespread acceptance of end-tidal carbon dioxide monitoring and mass spectrometry, MH is being detected earlier, and appropriate treatment instituted more promptly. Through such early recognition, and treatment with dantrolene, we can reasonably expect a further decrease in the mortality and morbidity of this enigmatic disorder.

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MALIGNANT HYPERTHERMIA: BIOCHEMICAL ASPECTS OF THE ACUTE EPISODE

J. J. A. HEFFRON

Early studies indicated that the pharmacogenetic disorder, malignant hyperthermia (MH), was inherited as an autosomally dominant trait in humans [3]. More recent interpretations indicate that MH may be inherited through more than a single gene [9, 10] and that the pattern of inheritance may vary from recessive to dominant. This uncertainty about the mode of inheritance of human MH has contributed to the confusion which abounds in biochemical studies of the molecular aetiology of the syndrome. It now seems unlikely that MH is caused by a single enzyme or protein lesion such as is seen, for instance, in McArdle's disease or phenylketonuria. While the nature of the genetic abnormality remains unclear, there is good evidence that the fundamental defect is located in the fibres of the skeletal musculature. For example: tubocurarine will not block induction of MH by halothane; muscular rigidity is one of the first signs of onset of an MH episode; the neuromuscular blocker dantrolene blocks development of the syndrome and halothane-induced contractures of biopsy strips of muscle from MH susceptible individuals; the resting intracellular free calcium ion concentration of MH muscle fibres is increased; and up to 70% of subjects show increased muscle-specific serum creatine phosphokinase activity [6, 16, 17]. Indeed, the so-called MH syndrome is now recognized as a metabolic disorder of skeletal muscle in the two major treatises on muscle disease [7, 21].

The clinical signs and symptoms of acute malignant hyperthermia have been described by numerous authors in case reports; briefly, the typical symptoms are rigidity, metabolic and respiratory acidosis, tachycardia, hyperkalaemia, hyperthermia and myoglobinuria. The severity and onset time of MH varies with the chemical nature of the volatile anaesthetic used and is usually more pronounced when used in combination with suxamethonium. The most marked, macroscopic symptoms are the skeletal muscular rigidity and rapid rate of increase of body temperature. The rigidity developed during MH onset appears not to be a regular form of contractile activity, but rather a pronounced contracture—that is, caused by a depolarization other than that initiated by a propagated action potential. The increased body temperature, which may reach 43–44 °C in the fulminant syndrome, is a consequence of an accelerated rate of energy metabolism. In the acute MH episode, it may be difficult to distinguish the exact sequence of events, and this is particularly true of the early biochemical changes. Fortunately, an excellent model of human MH was discovered in certain breeds of pig in 1966 [15]; since then it has been shown that the human and porcine MH syndromes are nearly identical with respect to changes in vital signs, muscular activity and metabolism [20]. Thus, our knowledge of the biochemical changes occurring in the acute MH episode are largely derived from controlled experiments on MH susceptible pigs and only to a lesser extent from case reports of acute episodes in humans. In the following paragraphs, I will attempt to explain in biochemical terms the nature of the features of the acute human MH episode, largely by liberal extrapolation of data derived from porcine MH studies by numerous researchers throughout the world. More detailed analyses of the early and recent literature on MH have been published in the reviews by Gronert [9, 10], Denborough [5], Ellis and Heffron [6] and Mitchell and Heffron [18]. Explicit analysis and discussion of published work attempting to identify the molecular aetiology of MH will be avoided in this review, but can be found in the paper by Ellis and Heffron [6].

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BIOCHEMICAL CHANGES AT TISSUE LEVEL

Skeletal muscle

The earliest detectable changes in the acute MH episode have been observed in the venous effluent from skeletal muscle; pH and Po_2 are decreased, while Pco_2 and lactate concentration are increased [8, 12]. These changes in the venous blood reflect earlier changes in the metabolic rate of skeletal muscle initiated by the triggering agent(s). No other tissue can produce such large amounts of lactate which can increase by up to 20 times the resting concentrations. Increase in blood lactate concentration has been shown to occur before any clear signs of tissue hypoxia are manifest. This finding remains an enigma. The presumed non-hypoxic lactate production by skeletal muscle might be caused by either or both of the following: (i) a block in the transport of pyruvate from the sarcoplasm into the mitochondria, thus preventing its oxidation via the tricarboxylic acid cycle; (ii) loss of inorganic phosphate from ATP breakdown in the muscle into the extracellular fluid.

The former explanation has not been examined experimentally, but the latter is the more probable, since it is already known that the plasma membrane of the muscle fibre becomes extremely permeable at the time of onset of acute MH [2]. The relevant changes noted by Berman's group were movement of Mg^{2+}, Ca^{2+} and inorganic phosphate into the extracellular space and plasma. The initial increase in membrane permeability may itself be caused by the massive depletion of creatine phosphate and ATP which occurs very early in the onset of MH, rather than to the decrease in pH, which has a slightly later time course [1, 13, 19]. Since MH is triggered in skeletal muscle by some as yet unknown process which increases the sarcoplasmic ionized calcium concentration, it appears likely that this calcium would activate membrane-associated phospholipases in addition to the contractile process. Such phospholipase activity would result in increased membrane permeability as fatty acid liberation progresses in the early minutes of onset of MH.

In the MH crisis, both aerobic and anaerobic metabolism increase dramatically before any detectable increases in temperature, heart rate and catecholamines are noted. The increase in whole-body aerobic metabolism has been shown to be a specific increase in the aerobic metabolic pathways of skeletal muscle, which accounts for some 40% of the body mass. This increase in metabolism represents an attempt by the muscle fibre to produce ATP at a rate sufficient to counteract the rate of ATP hydrolysis by actomyosin ATPase of the contractile apparatus, the process responsible for the rigidity which is so much an early feature of the MH crisis. At the peak of the crisis, there occurs a three-fold increase in oxygen consumption; this represents only a fraction of the maximal aerobic capacity of skeletal muscle, about one-sixth, in fact. Gronert [10] has pointed out the paradoxical nature of this small increase in relation to the large disturbance of acid–base balance and temperature alteration which occur. It would appear that there is a link between this phenomenon and the accumulation of lactate under non-hypoxic conditions; the explanation for the latter, already given above, would also account for the limited increase in oxygen consumption noted in the acute episode. At this time, it is reasonably certain that the functional deficiencies which have been observed in mitochondria from untriggered MH muscle [11] or the muscle fibre type cannot account for the attenuated aerobic metabolic rate in MH.

It is well known that, if the MH crisis is not actively treated as soon as it is diagnosed (and that is the real difficulty), the syndrome becomes irreversible. The point of irreversibility, which is difficult to determine even in the experimental situation, is probably the time at which the concentration of ATP in the muscle decreases to one-half of the resting concentration, for it is known from biochemical studies of normal muscle that rigor sets in when the energy status of the cell decreases to this value. From this stage of the acute episode, many other irreversible reactions occur, most notably increased breakdown of the mitochondrial membrane as the ATP concentration decreases to zero, and a further massive increase in plasma membrane permeability, leading to loss of larger molecules and proteins such as myoglobin. It must be emphasized that such a general increase in membrane permeability occurs because there is insufficient ATP and other nucleoside triphosphates (e.g. CTP) in the muscle fibre which are essential for the activity of the enzymes normally involved in the repair and maintenance of cell membranes. The concomitant acidotic conditions and high temperature will also cause membrane damage and a degree of denaturation of enzymes and other functional proteins. The high temperature itself will fluidize muscle cell membranes, an effect which will increase electrolyte and small molecule permeability. Unlike the situation in muscular dystrophy, calcium-activated proteinase activity does not appear to have a role in the aetiology of MH. This general increase in permeability of the skeletal musculature and the fact that it accounts for almost half of the total body mass indicates that the products of its extreme metabolic activity during the acute episode will initiate secondary MH responses in several other tissues.

Heart

Cardiac function is undoubtedly altered in the early stages of development of MH, as indicated by the occurrence of tachycardia and arrhythmias. Later on, hypotension develops and cardiac output continues to decline and eventually ceases. During porcine MH, a five-fold increase in myocardial oxygen consumption has been measured; this change can be blocked by infusion of propranolol indicating that it is a response to increased concentrations of circulating catecholamine, which in turn are most probably elicited by the metabolic acidosis generated by the skeletal muscle. Neither lactate production nor efflux of potassium ions is altered in the heart during an MH episode. It may be concluded, therefore, that the myocardial reponse is secondary to metabolic changes originating in the skeletal muscle. The continuing decline and ultimate cessation of cardiac contractility is most probably mediated by the hyperkalaemia caused by the progressive efflux of potassium ions from the critically metabolizing skeletal musculature. It appears unlikely that there exists any primary change in the myocardium of MH-susceptible individuals which predisposes an individual to MH. Nevertheless, it must be mentioned that the occurrence of non-specific cardiomyopathic changes has been reported.

Liver

In studies of hepatic metabolism in porcine MH [14], no major abnormality of liver function was detected. Although the rate of hepatic blood flow decreased during MH, there occurred a compensatory increase in oxygen extraction which enabled splanchnic oxygen consumption to be maintained. The liver released significant potassium ions and glucose and thus contributed to the hyperkalaemia and hyperglycaemia. The hepatic lactate pool did not contribute to the characteristic metabolic acidosis in MH; rather, lactate uptake by the liver was increased during the crisis. It would also be expected that the increased secretion of catecholamines, already referred to, would stimulate hepatic glycogenolysis and would therefore explain the hyperglycaemia observed by Hall and colleagues [14].

Nervous system

For obvious reasons, no direct experimental evidence of primary biochemical changes in the central nervous in MH have been made. In contrast to whole body oxygen consumption, cerebral oxygen consumption is not altered in the porcine MH crisis; similarly, the cerebral venous concentrations of lactate and potassium ions were not altered in MH. It is unlikely, therefore, that the central nervous system is involved in the primary pathogenesis of MH. A secondary involvement is indicated, but this is caused by the acidosis, hypoxia, high temperature and hyperkalaemia. In particular, the acidosis, hypoxia and hyperthermia would inhibit cerebral mitochondrial ATP synthesis and glucose oxidation by the glycolytic pathway and the tricarboxylic acid cycle, the metabolic processes upon which the brain so critically depends for the chemical energy which sustains neuronal electrical activity. The neurological changes in humans, such as coma, are readily explicable in terms of these projected biochemical changes.

In the case of the sympathetic nervous system, considerable controversy exists in the literature on the time-scale of the involvement of the catecholamines, adrenaline and noradrenaline, in the development of the MH crisis. Catecholamine concentrations in the blood are increased 30-fold during MH, but the increases appear to follow the stimulation of skeletal muscle metabolism. Such hormonal increases would further stimulate muscle glycogenolysis and cardiac and hepatic metabolism. Disagreement also exists on whether the resting metabolic rate in MH susceptible swine is altered; fortunately, the observations on MH-susceptible humans are clear-cut. Campbell, Ellis and Evans [4], in a comprehensive study of biochemical and physiological parameters in MH susceptible and normal individuals, found that there was no difference between the resting metabolic rate of the two groups. This observation indirectly supports the view that the catecholamines exacerbate, but do not initiate, the MH reaction. Theoretical biochemical analysis of metabolic control mechanisms also predicts that sympathetic activation on its own would not initiate the fulminant MH crisis; simultaneous, massive activation of ATP-degrading processes in skeletal muscle would also be required.

Blood

Unexplained acidosis, together with increased carbon dioxide pressure and decreased oxygen pressure, as measured by arterial gas analysis, are diagnostic indicators of an impending MH crisis. Metabolic acidosis caused by increased lactate production and respiratory acidosis caused by increased carbon dioxide production (cf. skeletal muscle section), both by-products of the escalating metabolism of the skeletal musculature, coexist. Total serum and ionized calcium concentrations increase during the porcine MH crisis; the increase in the latter is predictable when account is taken of the profound acidosis. The situation in the human MH crisis is unclear, because calcium-free i.v. therapy of human patients interferes with the measurement of actual total and ionized serum calcium during the acute episode. Serum potassium increases two- to three-fold during the MH crisis; it arises principally from the sarcoplasm, being released when the muscle cell membranes are damaged by both the acidity, high temperature and loss of ATP. The hyperkalaemia may cause heart block, which may progress to cardiac arrest and, ultimately, death. Sarcoplasmic proteins also leak from muscle fibres during the acute episode, but the time course of such leakage is somewhat later than that of electrolyte loss, presumably because of the greater molecular weights of the proteins. For instance it is well-known that myoglobin (molecular weight ca. 16000), the intracellular oxygen-carrying protein of red skeletal muscle, leaks into the circulation, resulting in myoglobinaemia. So too, does the enzyme creatine phosphokinase, the serum concentration of which may plateau only 24 h after the acute episode. Erythrocyte haemolysis can also occur during the acute episode; it is likely that it is caused by the acidosis, rather than by halothane or high temperature.

Kidney

Progressive loss of myoglobin from muscle and increasing myoglobinaemia is followed by myoglobinuria. This can lead to oliguria and eventually anuria, as the comparatively large protein molecules accumulate and ultimately block the pores of the basement membrane of the glomerular filtration barrier. This phenomenon can become more prominent when the patient has suffered an episode of hypotension. No biochemical data, direct or indirect, on the metabolic state of the kidney in the MH crisis are available. It is therefore not possible to say how renal tubular reabsorption would be affected in MH.

HEAT PRODUCTION

Much has been written of the metabolic origin of the heat which manifests itself as the characteristic temperature increase of the MH crisis. Contrary to early reports and suggestions, it now appears unlikely that the heat arises from uncoupling of the process of oxidative phosphorylation in the mitochondria of skeletal muscle. More recent studies indicate that most of the heat is generated by the rapid hydrolysis of high-energy phosphate compounds by actomyosin ATPase during contraction, by sarcoplasmic reticulum ATPase during relaxation, by the sodium pump enzyme system during membrane repolarization, by neturalization of hydrogen ions produced under the metabolic and respiratory acidotic conditions, by that proportion of the free energy released but not captured as ATP during the accelerated aerobic and anaerobic metabolism which occurs during the acute episode and, perhaps, by futile cycling of fructose-1, 6-bisphosphate to fructose-6-phosphate. Precise identification of the reactions producing the heat has not been possible, primarily because of the unsteady metabolic and circulatory states which prevail during the acute episode and because of uncontrolled heat losses [10].

RECOVERY FROM THE ACUTE EPISODE

The duration of postanaesthetic myalgia, myoglobinaemia and increased serum creatine phosphokinase activity indicates that complete recovery can take from a few days to a few weeks and that it is a function of the severity of the acute malignant hyperthermic episode. In biochemical terms, the enzyme systems which synthesize new membrane proteins and phospholipids and assemble them correctly in the membrane structure must be activated and provided with sufficient substrates so that the repair process can proceed at a maximum rate. Progress of repair will depend on the nutritional strategy adopted in the immediate postepisodic period. Clearly, if cells have been severely damaged, necrosis will set in; this applies particularly to neurones of the central nervous system, which are irreversibly damaged by anoxia lasting longer than about 4 min. Such anoxia causes neuronal ATP depletion and ionic equilibration and, consequently, permanent neurological damage. By contrast, skeletal muscle fibres can withstand sustained anoxic periods of 20–30 min by virtue of their anaerobic glycolytic capacity and the activity of the enzyme adenylate kinase.

GENERAL CONCLUSIONS

The acute MH episode is initiated by an abrupt increase in the intracellular ionized calcium concentration of skeletal muscle. This singular event sets in train a cascade of metabolic events which depletes the high-energy phosphate reserves of the muscles. If the cascade is not interrupted and arrested very early in the onset phase (for instance, by i.v. dantrolene therapy), an irreversible phase of very rapid metabolism, rigor development and destruction of muscle cell membranes is entered and the episode becomes fatal. Thus, MH may best be regarded as a myopathy in which the skeletal muscle has an impaired ability to regulate the intracellular ionized calcium concentration when clinical concentrations of potent volatile anaesthetics or certain neuromuscular blocking agents, or both, are present. The precise intracellular defect responsible for the loss of intracellular calcium homeostasis has not been identified; it still remains the elusive target of many biomedical researchers.

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DANTROLENE—DYNAMICS AND KINETICS

G. G. HARRISON

Although Bianchi's perceptive suggestion [2] at the First International Symposium on Malignant Hyperthermia in 1971, that diphenyl hydantoin should be investigated as a possible therapeutic agent for Malignant Hyperthermia (MH), did not bear fruit, it was the introduction of another hydantoin—dantrolene sodium—that later revolutionized the treatment and prognosis of MH. Dantrolene was synthesized originally by Snyder and associates [49] during the investigation of a series of substituted furans that had muscle relaxing properties, and its skeletal muscle relaxant properties were shown by Ellis and coworkers [11–13] to stem from a selective depressive action on the intrinsic mechanisms of excitation–contraction coupling (ECC). This demonstration motivated the successful therapeutic trial of dantrolene in porcine MH [24, 26], followed later by its equally successful use in the MH syndrome in man [32].

At the time this syndrome first came to world notice, during the decade of the 1960s, the mortality from MH was of the order of 80%. During the 70s, increasing awareness of the syndrome with resultant earlier diganosis and treatment, albeit non-specific, led to an improvement in prognosis, recorded mortality decreasing to 28%. This decade, following the introduction to practice of dantrolene sodium, the mortality recorded following MH is now but 7% and these subjects, on review, all manifested serious avoidable errors in therapeutic management. Today, with correct management utilizing dantrolene sodium, survival from MH is the expected norm [4, 23].

Chemistry

Dantrolene sodium, 1-{[5-(p-paraphenyl) furfurylidene] amino} hydantoin, is pharmacologically the most active member of a long series of 1-[(5 aryl furfurylidene) amino] hydantoins synthesized for their muscle relaxant properties (fig. 1). Dantrolene is the only analogue in the series to achieve clinical usage, although others have been tested [51].

The molecular structure of dantrolene is planar, with the exception of the phenyl ring, which is rotated approximately 30° out of the plane of the furan ring [13] (fig. 1).

Highly lipid soluble, but extremely poorly soluble in water, the drug was originally dispensed in capsular form for administration by mouth—a circumstance compatible with its originally envisaged use for the pharmacological control of chronic states of muscle spasm. Once its efficacy in the control of MH had been demonstrated, its wide-spread use for this purpose was sadly delayed some years by the need to develop an i.v. formulation appropriate to the clinical circumstances of MH.

Today, for this purpose, the drug is supplied in ampoules containing 20 mg of lyophylized dantrolene sodium, an orange powder, together with mannitol 3 g (which improves the solubility) and sufficient sodium hydroxide to yield a pH of 9.5 when the contents are dissolved in 60 ml of water. The final concentration of dantrolene in this solution is 0.33 mg ml^{-1}.

Pharmacodynamics

The primary pharmacological action of dantrolene is the relaxation of skeletal muscle, with reduction in the force of contraction. This, although dose-dependent, reaches a plateau at a level well short of total paralysis of muscle, regardless of the dose [21]—a circumstance attributed to the limited water solubility of the drug [13].

The loci at which drug action could have such an effect in the complex interactions responsible for skeletal muscle contraction are shown diagrammatically in figure 2 and provide the background against which will be presented findings, from the extensive investigation to which dantrolene has

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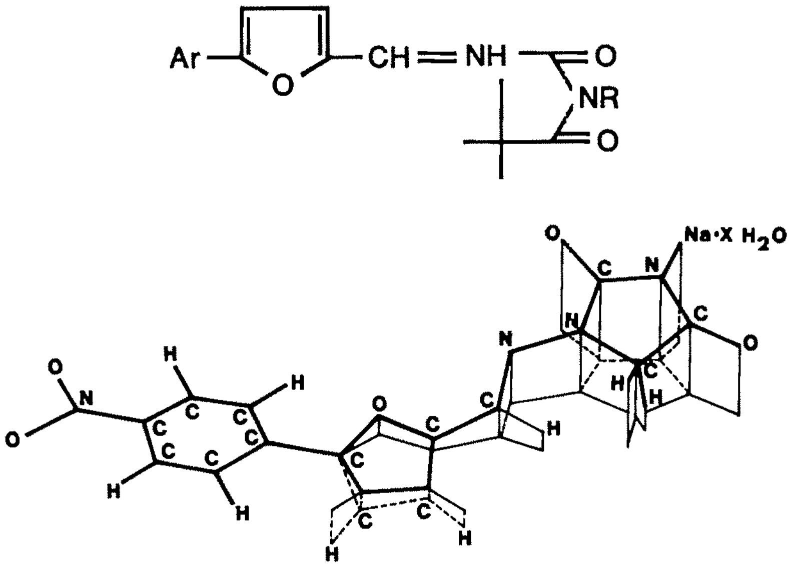

FIG. 1. Top: Structural formula of derivative aryl amino hydantoins. Below: Ground state conformation of 1-{5-(p-nitrophenyl) furfurylidene} amino hydantoin sodium hydrate: dantrolene sodium.

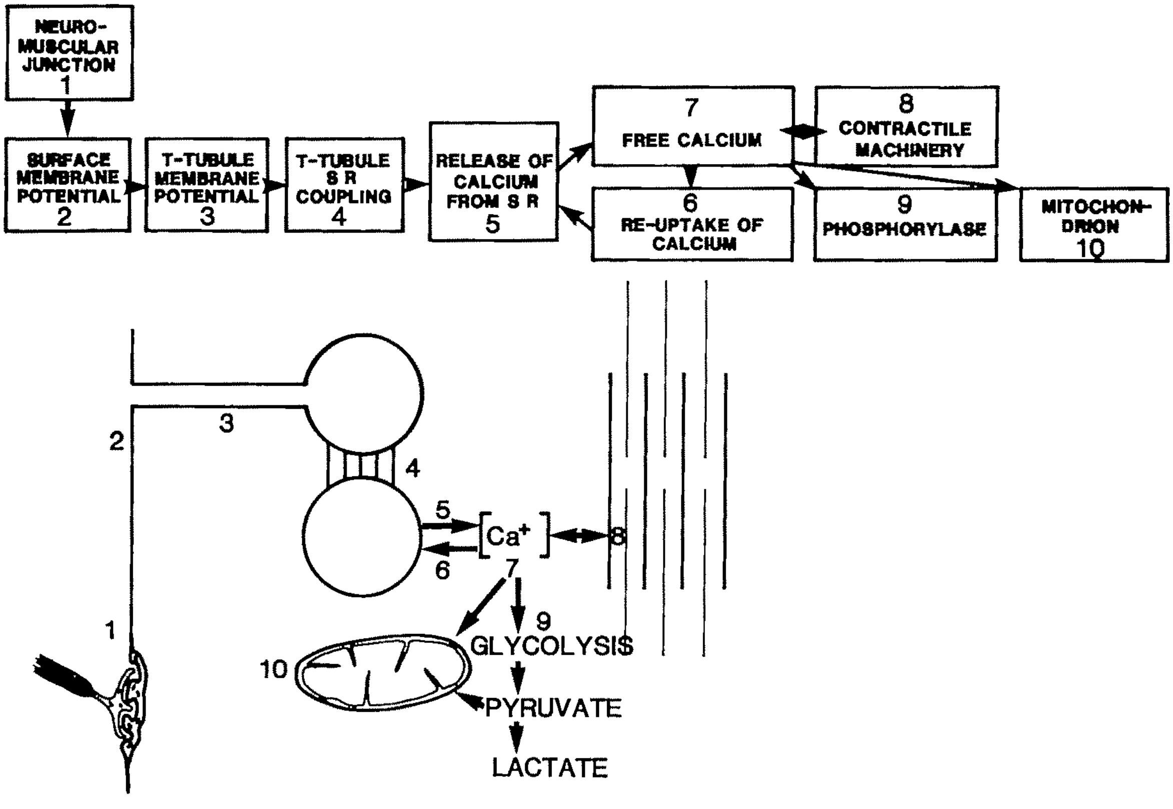

FIG. 2. Sequential steps in skeletal muscle excitation–contraction coupling.

been submitted, that are most relevant to our present understanding of its mode of action.

Early work, predominantly that of Ellis and associates [11–13] showed the relaxant action of dantrolene to be unusual and to result from a depressive action within the muscle cell at one or more loci in the ECC train, specifically affecting the sarcoplasmic reticulum (SR). Briefly, these conclusions were based on observations that dantrolene:

(1) did not act on the CNS [13,56];

(2) had no effects on spinal polysynaptic reflex responses [13];

(3) acted directly and specifically on skeletal muscle and had no effect on cardiac or smooth muscle, nor did it affect respiration ventilation [13,15,21];

(4) had no effect on the neuromuscular junction [5,13,56] and produced no change in "train-of-four" ratios [21];

(5) had no effect on the electrical properties of sarcolemma or T-tubular mechanisms, nor was the EMG affected [13,35];

(6) caused dissociation of muscle ECC by interfering directly with SR calcium release or the preceding "trigger calcium", or both. These deductions, based originally on observation of the interactive effects of dantrolene with those of caffeine, procaine and EDTA on *in vitro* induced muscle twitch and tetanus [13], were confirmed by the direct observation by van Winkel [55] and Desmèdt and Hainout [7] that dantrolene reduced SR calcium release, both in rate and amount, without completely abolishing it. Ellis and Carpenter [13] postulated that the effect on trigger calcium might be the basis for the specificity of action of dantrolene on skeletal muscle, as opposed to its lack of action on cardiac and smooth muscle, in which sarcolemmal calcium transients constitute the more important mechanism in ECC;

(7) had no effect on SR calcium uptake [13,53, 55].

Morgan and Bryant's conclusions [39] based on the foregoing and their own observations of the effects of dantrolene on rheobasic potential, chronaxie and on voltage dependent "charge movements", provided the best concept, at that time, of the mode of action of dantrolene. They proposed that dantrolene acted to cause skeletal muscle relaxation by interference with ECC at no fewer than two sites, the SR membrane and the voltage-dependent "charge movements" of the T-tubular–SR coupling. At the first site the effect is to decrease the release of calcium out of the SR, possibly by decreasing the mobility of a natural calcium ionophore. At the second site the effect is produced by an increased rate of movement of the "charge movement particles" to the OFF position.

Whatever its mechanism, depression by dantrolene of the rate and amount of SR calcium release finds its most dramatic expression in the abrupt termination of the MH syndrome it engineers—illustrated in figures 3 and 4 by animal biochemical and human clinical data [24,29]. This action,

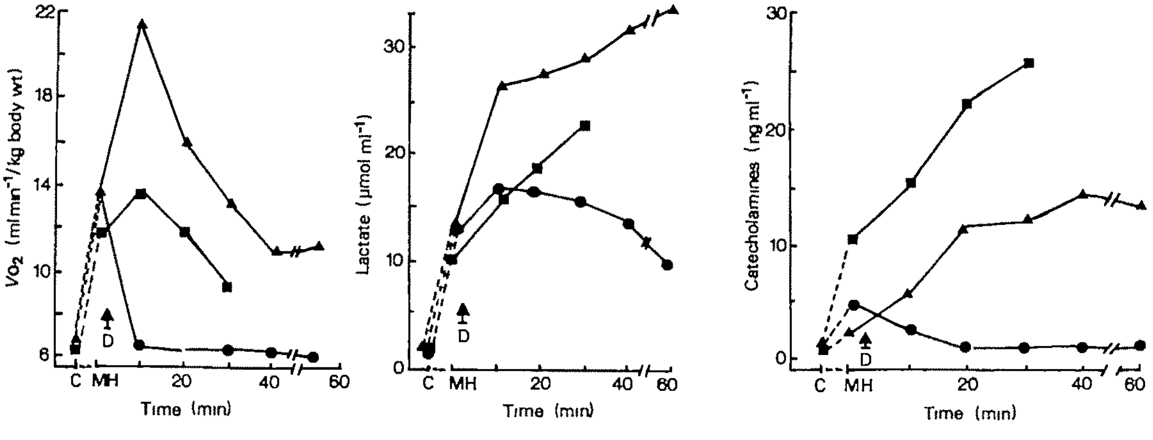

FIG. 3. Effects of dantrolene administration (D) on the $\dot{V}o_2$, lactate production and catecholamine secretion of MHS swine provoked into malignant hyperthermia by anaesthesia with halothane. ■ = Untreated; ▲ = supportive treatment only; ● = supportive treatment and dantrolene 7.5 mg kg^{-1}. (From Gronert, Milde and Theye [24] with permission.)

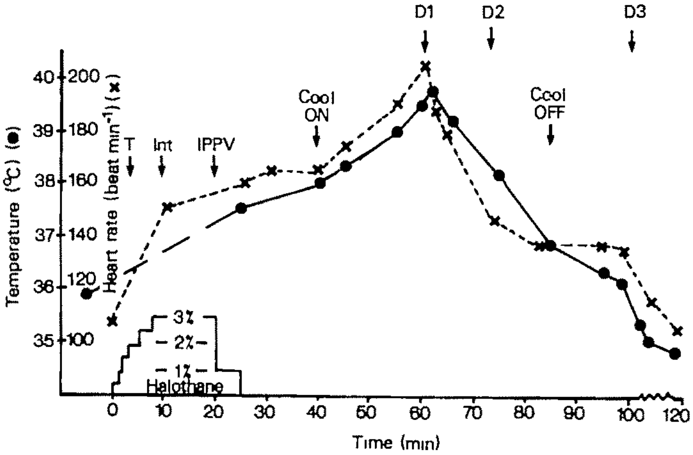

FIG. 4. Malignant hyperthermia: illustrative events chart from a 9-yr-old female patient admitted with congenital kyphoscoliosis (see associated conditions), for insertion of Harrington Rods. Note: Onset tachycardia; progression of syndrome despite discontinuation of halothane and institution of cooling; immediate response to dantrolene (delay in administration occasioned by its being obtained from neighbouring hospital). The operation was successfully performed 6 weeks later, when prophylactic i.v. dantrolene was given with induction. T = Thiopentone; Int. = intubation. Cool ON = Start of cooling; Cool OFF = discontinuation of cooling; D1, D2 = dantrolene 1 mg kg^{-1}; D3 = dantrolene 0.5 mg kg^{-1}. (From Harrison and Chapman [29], with permission).

which has been shown by direct measurement by Lopez [37] to correlate with a dantrolene-induced decrease in myoplasmic free calcium, has the attributes of the turning off of a switch and itself carries implications for both the pathogenesis of MH and the mode of action of dantrolene. Considered together with observed lack of effect of dantrolene on SR calcium uptake, it implies that continued SR calcium release—as against decreased SR uptake—is fundamental to the genesis of MH. Once this is terminated, the function of other calcium modulating mechanisms appears adequate to return myoplasmic free calcium to resting concentrations, permitting relaxation of muscle and termination of the syndrome.

An attractive current hypothesis identifies an abnormality in the mechanism of calcium-induced calcium release (CaIR) from the SR as the causative functional lesion of susceptibility to MH [16, 17]. This putative third SR calcium channel, which has no physiological role in the mechanism of skeletal muscle contraction, has been shown to have a lower than normal threshold and to respond with a faster than normal rate of calcium release, in subjects susceptible to MH [31]. As some similarity had been demonstrated between caffeine (and halothane) and CaIR [16], it seemed not unreasonable to expect that dantrolene would decrease the latter, as it has been shown to inhibit the former [13, 43].

This, however, has not proved to be the case [40]. Examining the effects of dantrolene on SR calcium release induced by caffeine, calcium jump and depolarization, Danko and colleagues [6] showed these to be complex and clearly distinguishable from those of the conventional SR calcium channel blocking drugs such as amethocaine and procaine, which inhibit all these modalities equally [1]. While inhibiting caffeine- and halothane-induced SR calcium release, dantrolene produced no effect on CaIR and exhibited a time-dependent dual effect on depolarization-induced calcium release—an initial inhibition being followed by enhancement. Associated with these findings was a correlative pattern in the binding of dantrolene to both SR and T-tubular membranes. Two kinetically distinguishable binding sites were identifiable on the T-tubular membranes, the slow binding site being related to the effects of the drug on depolarization-induced calcium release. Of that portion which bound to the SR, little competed with caffeine binding sites, suggesting that much of the binding of dantrolene was to non-specific sites unrelated to calcium release.

Considering the above in the light of their therapeutic activity in the MH syndrome, one may speculate that the difference between the uncertain action of the conventional SR calcium-blocking drugs such as procaine and the completely reliable action of dantrolene [28] must lie in the latter's more complex action involving, as it does, a major effect on the T-tubular–SR coupling mechanism. Such a postulate carries its own implications for the conceived pathogenesis of MH.

In this regard it is important to note that, while dantrolene has no effect on normal sarcolemma, its action on the sarcolemma of MHS muscle is of relevance. Gallant, Godt and Gronert [22] have demonstrated that, whereas exposure to halothane has no effect on the sarcolemma of normal muscle, that of MHS muscle responds to such exposure by a depolarization of between 5 and 15 mV—a reaction that is antagonized by dantrolene. While this degree of depolarization, with its accompanying increase in calcium permeability, would not be sufficient of itself to initiate contraction in normal muscle, it could so do in the presence of SR that displayed a low threshold CaIR mechanism such as is postulated to characterize MHS muscle [44].

All in all, therefore, it seems that, although dantrolene provides a specific and life-saving treatment for the syndrome of MH, we are still a long way from understanding the finer details of its mode of action and, correspondingly, those of the pathogenesis of MH.

Effective antagonism of the muscle relaxant properties of dantrolene sodium is provided by germine monoacetate (GMA) [34].This reversal follows no direct pharmacological antagonism, but is the result of the property of GMA in causing repetitive firing of muscle in response to single stimulation and, so, repetitive myoplasmic free calcium release. In essence, it produces the effects of a brief tetanus, which is well documented as being depressed by dantrolene less than single twitch [13, 42].

Pharmacokinetics

Following its ingestion by mouth, approximately 70% of dantrolene is absorbed, peak plasma concentration being reached in 6 h [10]. However, especially in children, there is great variation between patients in the plasma concentrations achieved relative to the oral dose [36]. This fact doubtless accounts for the reported failure in prophylactic efficacy for MH of dantrolene administered by mouth [19, 47].

After i.v. administration of dantrolene to the conscious patient, the plateau maximal depression of muscle twitch response (75% depression) and the maximal depression of grip strength (42% depression) coincides with the administration of an accumulative dose of 2.4 mg/kg body weight. This achieves a blood dantrolene concentration of 4.2 $\mu g\ ml^{-1}$. Thereafter the elimination half-life ($T_{\frac{1}{2}}^{\beta}$) is 12 h, although the blood concentration is maintained at a steady value within the therapeutic range for about 5 h. Residual dantrolene concentration in the blood at 24 h after such a dose is 1.7 $\mu g\ ml^{-1}$ and this is reflected subjectively by patients, in a feeling of weakness. This may persist for up to 48 h, by which time the residual blood concentration of dantrolene has decreased to 0.3 $\mu g\ ml^{-1}$ [21].

Dantrolene is microsomally metabolized in the liver, through both oxidative and reductive pathways. The former results in hydroxylation of the hydantoin ring to form 5-hydroxydantrolene (5HD), while reduction of the nitro- moiety of the benzene ring results in the formation of aminodantrolene, which is then acetylated to form the reduced acetylated derivative of dantrolene (RAD) [36]—metabolites which themselves manifest some muscle relaxant properties [14].

Excreted in both the urine and the bile, dantrolene is 79% excreted as 5HD, 17% as RAD, while 4% of the dose appears unchanged in the urine [10, 36].

Adverse effects and drug interactions

Although dantrolene is documented as having no effect on the CNS, the commonest adverse reactions it causes are symptoms of dizziness, lightheadedness and drowsiness. These feelings can accompany both acute i.v. and chronic oral administration of the drug [21, 36]. There is, as yet, no suitable explanation for these changes in the sensorium. It is suggested that they may exemplify similar changes in the sensorium reported to accompany inhibition of neuromuscular transmission *per se* by other drugs [21]. While these unpleasant side effects may be associated with nausea and vomiting, the latter more commonly follows oral ingestion of the drug, in which case they may be accompanied by diarrhoea [10].

The major adverse reactions that have been documented following administration of dantrolene, have all accompanied its chronic administration by mouth. Perhaps most important have been reports of hepatic dysfunction [18, 45, 54].

However, several reports to the contrary lead one to question whether the drug alone was responsible for the hepatic dysfunction observed. To cap the reports of Dykes [10] of no change in serum biochemistry, urine function or haematological indices following prolonged administration by mouth, and the failure of Flewellen and colleagues [21] to find any change in SGOT and SGPT concentrations to accompany acute i.v. administration of dantrolene, Durham, Gandolfi and Bentley [9] have reported their failure to produce any evidence of dantrolene hepatotoxicity in mice, even after enhancement of any hepatotoxic potential by the inhibition of acetylation, depletion of glutathione, induction of biotransformation and the promotion of reductive metabolism. Further, Sorensen and Acosta [50] have failed to produce in hepatocyte cultures any evidence of hepatotoxicity from dantrolene.

Other adverse reactions include reports of the relatively common and non-specific drug reaction of an acneiform rash associated with prolonged oral ingestion of dantrolene [10].

The most important adverse interaction of dantrolene with another drug is that with verapamil—a drug which may be considered indicated in the management of MH associated-cardiac tachyarrhythmias. While dantrolene alone has no myocardial effects, Saltzman and others [48] and Lynch and colleagues [38] reported marked myocardial depression in swine and dogs after administration of verapamil in the presence of dantrolene, and *vice versa*. Although this reaction has yet to be described in man, simultaneous administration of verapamil and dantrolene should be regarded as contraindicated in any event, as the cardiac arrhythymias that accompany MH invariably respond to the termination of the syndrome with dantrolene and correction of the associated acidosis and hyperkalaemia.

As dantrolene causes a decrease in the force of muscle contraction, some mechanical synergism with drugs which block neuromuscular transmission can be expected. Driessen, Wuis and Gielen [8] reported an unexpected interaction of dantrolene with the non-depolarizing neuromuscular blocking agent, vecuronium, in which the presence of dantrolene caused marked prolongation of the neuromuscular junction recovery time as monitored by the evoked EMG—a modality not normally affected by dantrolene. They speculated that this effect may result from decreased transmitter mobilization at the neuromuscular junction because of impairment of calcium release from storage sites within the cholinergic terminals. Little more can be said of this reaction until there has been considerably more investigation.

Therapeutic use of dantrolene

Dantrolene was originally introduced to therapeutics for the long term functional control of chronic states of skeletal muscle spasm such as follow stroke or characterize cerebral palsy. That it may still have some use in this regard is born out by the very favourable report from Ketel and Kolb [30] of its successful long term use in the treatment of stroke patients with spasticity limiting return of function.

However, the most important therapeutic use of dantrolene today is in the treatment of MH, in which circumstance it is indeed life-saving [23]. It has now proved equally life-saving in the management of the functionally related neuroleptic malignant syndrome [25]. More recently, its use has been suggested as an adjunct in the treatment of tetanus, especially at the stage at which the patient is weaned from conventional neuromuscular blocking and antispasmodic drugs [52].

For i.v. use, dantrolene is supplied as an orange powder (together with sodium hydroxide and mannitol), in a vial containing 20 mg, which is dissolved by the addition of 60 ml of water. The resulting solution, pH 9–10, is irritant to veins and should be injected to a fast-running i.v. infusion or large vein. Effective therapeutic concentrations of dantrolene for the treatment of MH are achieved after the administration of 2.4 mg kg^{-1}. If necessary, this dose may be repeated at 15-min intervals, until relaxation of muscle rigor, control of tachycardia and arrhythmia and cessation of temperature increase are achieved, or a total dose of 10 mg/kg body weight has been given. It is seldom that a dose exceeding 4 mg kg^{-1} is required.

Although patients may complain of muscle weakness even up to 48 h after administration, this will not be of an order which imperils ventilatory capacity, or coughing.

Once controlled, the MH syndrome may recur in the post-anaesthetic period. Dantrolene administration should be repeated immediately at the first sign of such occurrence. In view of this possibility, some advocate a repeat prophylactic dose of dantrolene 2.4 mg kg^{-1} after 10–12 h—the elimination half-life of the drug.

In the treatment of MH, it must be emphasized that after a timely administration of dantrolene, after early diagnosis, little or no supportive therapy is necessary. The need for therapy is directly, perhaps exponentially, proportional to the delay in diagnosis and the institution of treatment. Such supportive measures and the treatment of MH generally are dealt with elsewhere in this issue and will not be discussed further here.

Following control of the syndrome the patient must be closely monitored and sedated for 24 h after initial recovery, for fear of recurrence of the syndrome.

Pre-anaesthetic prophylactic dantrolene for the MHS patient

The application of simple guidelines will ensure safe anaesthesia for the individual known to be susceptible to MH. These guidelines are:

(1) Obtundation of the patient's "trigger" sensitivity.
(2) Utilization of meticulous vital function monitoring.
(3) Avoidance of agents known to trigger MH.
(4) Immediate availability of i.v. dantrolene.

While it once seemed obvious that the prophylactic administration of dantrolene was the necessary and most efficacious way of achieving the first of these desiderata [27], this is now subject to some controversy. Certainly, the use of oral pre-anaesthetic prophylactic dantrolene regimens [3]—which may involve admission to hospital for a 2–4 day programme of administration of the drug, from which the patient may suffer many unpleasant symptoms and which does not guarantee prophylactic systemic blood concentrations of dantrolene [19, 20, 47]—are no longer to be recommended. Indeed, given the application of correct anaesthetic technique with meticulous vital function monitoring, together with the immediate availability of i.v. dantrolene, many would question the necessity for the prophylactic administration of dantrolene at all, especially if the planned surgical procedure is relatively short. However, when the surgery contemplated is prolonged, there are those who still think the patient's best interests are served if dantrolene is administered prophylactically. In these circumstances, it should be administered i.v. in a dose of 2.4 mg kg^{-1} during the induction of anaesthesia and—to avoid unpleasantness for the patient—after consciousness has been lost [29]. When this regimen is adopted, it must be noted that the effect that pre-anaesthetic prophylactic dantrolene might have on the outcome of *in vitro* contracture testing of muscle biopsied in these circumstances, is controversial. While, *a priori*, an invalidating inhibitory effect on both caffeine- and halothane-induced contractures is to be expected, and indeed has been reported [3, 33], the contrary has also been documented [41, 46]. These reported discrepancies are in all probability dose (and tissue concentration) dependent.

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DIAGNOSIS OF SUSCEPTIBILITY TO MALIGNANT HYPERTHERMIA IN MAN

H. ØRDING

The reported incidence of clinical malignant hyperthermia (MH) varies, but is altogether fairly low [14, 30, 79, 94, 108]. The need for elective diagnosis of susceptibility to MH, however, is by no means a rare phenomenon. This is first of all because susceptibility to MH is inherited [24], but also because anaesthetists, with the increasing awareness of MH, tend to terminate an anaesthetic if early signs of possible MH occur [31, 49, 127]. This increases the number of patients whose MH status cannot be determined from clinical data alone, but must be established from a diagnostic test.

Many diagnostic procedures have been described over the years, but only few have stood the test of time. Since we do not yet know if clinical MH is caused by one single biochemical defect or by various combinations of several defects, a definitive test for MH susceptibility has not been developed. Moreover, we do not know if the biochemical defects causing MH are the same in man and the pig. Since pigs often are inbred for susceptibility to MH, it seems unwise to extrapolate results obtained in pigs for uncontrolled application in man, therefore I will concentrate on investigations in humans in the following, although we have learnt much about MH from studies of pigs. In relation to diagnostic tests for susceptibility to MH, this creates problems. It is easy to apply a test for MH in pigs and subsequently challenge the animals with halothane and suxamethonium and get a definite answer. In humans, all evidence of accuracy and specificity is indirect, but should nevertheless be obtained. Thus any diagnostic test, before being introduced for general use, should be applied in patients with a previous history of unequivocal, fulminant MH as well as in normal control subjects. If complete separation of these two diagnostic groups is obtained with the test considered, it can be relied on for use in other groups of patients. This simple rule, unfortunately, has been followed for only a few of the described tests.

TESTS ON BLOOD

Serum tests

Creatine kinase. When MH was first recognized as a skeletal muscle disease, determination of creatine kinase activity (CK) was introduced as a diagnostic tool for MH susceptibility [23, 68, 69]. There is no doubt that CK is increased in many individuals susceptible to MH, but in others it is normal [56, 116]. Since increased CK activity is a non-specific sign of muscle injury, it may be increased as a result of factors other than MH. Many studies now show that, although MH susceptible individuals as a group have higher CK values than non-susceptible individuals, determination of CK is unreliable as a predictor of MH susceptibility in the individual patient [3, 11, 28, 96, 113, 116, 134].

Cholinesterase. For some years it was considered a possibility that inheritance of the fluoride resistant gene for plasma cholinesterase and susceptibility to MH were coupled. This was originally based on findings in a few families by Whittaker, Spencer and Searle [146], whose observations were confirmed by Ellis and colleagues [27]. While Whittaker later confirmed her original findings in a larger series of patients [145], Evans and co-workers from the Leeds group were unable to repeat their results, when performing a prospective study on a larger patient population [44]. Likewise, Ørding, Hanel and Viby-Mogensen [111] did not find any increased frequency of the fluoride resistant gene in MH patients. There may be two explanations for these

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discrepancies: The patient populations could be different, since susceptibility to MH was confirmed with *in vitro* contracture tests in two of the studies [44, 111], but not in the third [145]. In the latter study, analysis of cholinesterase was performed at the request of anaesthetists from different parts of Britain, and clinical details were not given. Another explanation could be the difficulty in correctly classifying cholinesterase genotypes containing the fluoride resistant gene [61]. In Denmark, cholinesterase genotype has now been determined in 249 patients suspected of susceptibility to malignant hyperthermia, and only two have been found with the fluoride resistant gene. This gene frequency is not statistically different from that found in the general Danish population [61]. Thus the evidence is not convincing for any correlation between cholinesterase abnormalities and MH.

Erythrocyte tests

Osmotic fragility. Increased osmotic erythrocyte fragility has been observed in some human subjects with MH [75], but decreased fragility has also been found [151], invalidating this test for diagnosis of susceptibility.

Chemiluminescence. The method of chemiluminescence for quantitating auto-oxidation in red blood cells has been described to give different results in MH susceptible and non-susceptible pigs [77]. Recently, Jones and Bready [72] were able to distinguish between diagnostic groups of pigs with known MH genotype using the ratio of chemiluminescence in erythrocytes before and after exposure to halothane. So far, no results with this test have been obtained in humans, although a defective protection against oxidant action has been observed in some survivors of MH [138].

Platelet tests

Platelet aggregation. Since platelets resemble skeletal muscle in that they contain calcium storage vesicles, contractile elements and a calcium dependent ATPase, platelets have been investigated in the search for a non-invasive test for MH susceptibility. One test based on platelet aggregation was suggested by Zsigmond, Penner and Kothary [151], but was not found useful for diagnosis of MH susceptibility by others: Rosenberg and co-workers studied platelet aggregation in five subjects with either a personal or family history of MH. All were found to be MH susceptible based on *in vitro* contracture tests with halothane and caffeine, and all but one exhibited normal platelet aggregation as compared with 23 normal control subjects [126]. Similar results were obtained by Sullivan, Ardlie and Denborough [136]. Gerrard and colleagues studied platelet aggregation in response to halothane in seven patients suspected of malignant hyperthermia and 35 normal controls [53]. They found that halothane (in concentrations far greater than those attained in blood during clinical anaesthesia) stimulated platelet aggregation in both MH patients and normal controls. Although the results of this study may be questioned because muscle biopsies were not performed in these patients and clinical data on the MH episodes were lacking, platelet aggregation tests do not seem useful for diagnostic purposes.

Platelet nucleotide depletion. This test was developed by Solomons and Masson [133]. The idea of the test involves two assumptions: that platelets are affected in MH, and that halothane decreases nucleotide content more in affected than in normal platelets, as a result of increased metabolism and ATP turnover in the MH subjects. The authors obtained very good diagnostic separation between patients with previous clinical MH and normal control subjects with this method. Later, this test has been evaluated in three independent studies [16, 54, 84], all of which concluded that this test is not useful for diagnosis of MH susceptibility, since halothane reduces nucleotide content of platelets equally in MH and control subjects. Although clinical and laboratory criteria for MH susceptibility varied in these studies, enough details were presented in all of them to make the conclusions valid. It seems unlikely that possible minor differences in technique should account for this lack of sensitivity of the platelet test, as has been claimed [132]. Should it be the case, however, such a test could not be recommended for large scale use, since the risk of wrong diagnosis because of technical difficulties would be unacceptably high. Hence the platelet test should not be used as a single diagnostic tool. It is not yet settled if platelets are indeed involved in human MH.

White cell tests

Human leucocyte antigen (HLA) type. Lutsky, Witkowski and Henschel [88] investigated the possible association of HLA type and MH susceptibility in one large family with several deaths attributed to MH. They did not find any association between MH susceptibility and HLA type in this Wisconsin family. On the other hand, Kikuchi and co-workers [78], in a preliminary report described that three out of four MH patients had an identical DR gene, which is not common in Japan. These patients were all MH probands and apparently not related. This observed association still awaits further investigation.

Calcium concentration in lymphocytes. By measuring the fluorescence of the calcium ion indicator quin 2, which was loaded into lymphocytes, Klip and colleagues [80] found that exposure of the lymphocytes to halothane increased the ionized calcium concentration significantly in cells from MHS patients, but not in cells from controls. The values after exposure to halothane were significantly different in the two groups, and there was only little overlap between the groups. This promising, fairly non-invasive test was also evaluated in pigs, where similar results were obtained [81]. In both studies, the concentration of halothane used (38 mmol $litre^{-1}$) was much greater than clinical concentrations. It was stated that halothane 1 mmol $litre^{-1}$ would also elicit an increase in calcium concentration, but results were not given. It will be very interesting to see if similar results can be obtained with this method in other MH centres, since a non-invasive test for MH is obviously much needed.

ELECTROPHYSIOLOGICAL TESTS

Motor unit counting

In 1977 Britt and colleagues described a test based on counting the number of functioning motor units in different muscles [15]. MH patients were found to have a reduced motor unit count compared with control subjects. The sensitivity of this test was found to be high in patients with a previous episode of rigid MH and in their relatives, but low in patients with previous non-rigid MH (but only three were investigated). It was noted, however, that the test was non-specific, and that abnormally low motor unit counts were seen in other myopathies and in denervating conditions as well. Conventional electromyography was also evaluated and found much less sensitive for the diagnosis of MH susceptibility than motor unit counting. Apparently, motor unit counting is not in use any more for diagnosis of MH susceptibility, and has not been further evaluated for this purpose.

Tourniquet test

Stimulation of a motor nerve and recording of the elicited mechanical twitch response has become routine for clinical monitoring of neuromuscular blockade during anaesthesia [142]. The same method has been applied for diagnosis of MH susceptibility by Roberts, Ali and Ryan [123], who recorded twitch height before, during and after ischaemia of the arm. MH patients were found to have an increased twitch height after ischaemia, whereas twitch height was unchanged or lower in normal controls. This "tourniquet test" has subsequently been evaluated by Britt and co-workers [18] in a large series of patients who also had *in vitro* contracture tests performed. Britt's group found it impossible to discriminate between susceptible and non-susceptible patients using the tourniquet test. They observed a tendency for young people to have increased and for old people to have decreased post-ischaemia twitch height. Since many of the MH patients in the study of Roberts, Ali and Ryan [123] had been children and the controls mostly adults, Britt and colleagues ascribed the results of the original study to a difference in age between the MH patients and the control group.

Relaxation rates of the elicited twitch response

Recently, Lennmarken, Rutberg and Henriksson [86] reported that relaxation rates of the elicited twitch response in the adductor pollicis muscle were significantly higher in subjects susceptible to MH than in normal controls. Because there was overlap in results between the groups, however, this interesting observation cannot be used for diagnosis of susceptibility without further standardization of the technique.

Recruitment pattern after halothane and suxamethonium

A fourth electrodiagnostic test was developed by Eng, Becker and Muldoon [41]. They investigated the EMG recruitment pattern of the hand muscles during maximal contraction before and after local instillation of halothane and suxamethonium. A significant decrease in the number of negative peaks of motor unit potentials was observed after instillation of suxamethonium in both MH subjects and normal controls.

However, the number of these potentials was significantly less in the MH susceptible individuals than in the controls. In nine subjects *in vitro* contracture tests were also performed, and in eight the results of *in vivo* and *in vitro* tests showed good correlation. Following these promising results, a larger, prospective study was planned, but has not yet been published; neither has this *in vivo* test been evaluated by other groups.

BIOCHEMICAL MUSCLE TESTS

ATP depletion

ATP depletion in muscle upon exposure to halothane was first described in 1969 by Harrison and co-workers [64], who could predict susceptibility to MH in pigs with this test. The ratio of ATP content in muscle before and after equilibration with halothane was determined and found decreased in pigs susceptible to MH. The test has been evaluated in humans by Britt and others [10]. They found the ratio to decrease with increasing age and therefore introduced an age correcting factor. Because of overlap between groups, they found it a less accurate method for diagnosis of susceptibility to MH than the caffeine contracture test. Sporn [134], using the halothane contracture test for diagnosis of MH susceptibility, also found the ATP ratios to overlap between MH susceptible and non-susceptible patients. In a study of normal human muscle, Gronert found that the ATP ratio was not decreased after exposure to halothane [57]. In contrast to Britt and others [10], Gronert [57] found no variation in ATP ratio with age. The reason for this discrepancy has not been elucidated, but is not very important, because of the lack of accuracy and specificity of the ATP depletion test.

Glycolytic metabolites

Indications of increased glycolytic activity in unstressed MH susceptible humans have been presented [29, 70], but were not confirmed in a more recent study, using an electrophoretic micromethod (isotachophoresis) on freeze clamped muscle tissue [141]. In another study, metabolites were determined before and during exercise [129]. MH susceptible subjects were found to have completely normal muscle metabolism. Hence the general metabolic pattern with or without stress cannot be used diagnostically.

Myophosphorylase ratio

The activated form of phosphorylase stimulates glycogenolysis in muscle and, ultimately, lactate formation, which is a prominent feature of clinical MH. Ono and colleagues therefore studied the content of phosphorylase a (the active form) in relation to the total content of this enzyme in pigs and found that this ratio was increased in stress susceptible pigs [107]. An even more increased ratio was found in humans susceptible to MH, in a study by Willner and co-workers [148]. They could predict susceptibility to MH from this test because there was no overlap in phosphorylase ratio between the MH susceptible and the control group. Susceptibility was diagnosed with either a single fibre caffeine test or a muscle bundle caffeine or halothane–caffeine test (*vide infra*). Ellis and colleagues [33] also found an increased phosphorylase ratio in MH susceptible patients (with overlap between groups), whereas Trayner, Van Dyke and Gronert were unable to confirm this finding [139]. It is not clear whether these observed differences are attributable to variations in the applied methodology (for example anaesthesia) or to the patient populations studied. However, increased sympathetic activity will activate phosphorylase and thereby influence the results. Since the stress factor is uncontrollable, phosphorylase ratio is probably not a very sensitive diagnostic test.

Adenylate kinase deficiency

In 1974 Schmitt, Schmidt and Ritter [130] reported a deficiency of adenylate kinase in the mother and a sister of two children, who died from MH. Since adenylate kinase plays an important role in maintaining adequate concentrations of ATP in tissues, the authors suggested that development of MH was the result of decreasing concentrations of ATP, when individuals with hereditary adenylate kinase deficiency were exposed to halothane. This theory was later rejected by Cerri and co-workers [21] and Marjanen and Denborough [91], who found normal adenylate kinase activity and isoenzyme pattern in humans susceptible to MH.

Adenylate cyclase activity and cyclic AMP

Adenylate cyclase is located in transverse tubuli and sarcolemma of skeletal muscle and indirectly mediates calcium transport in sarcoplasmic reticulum. Willner, Cerri and Wood [147] found increased activity of this enzyme in patients susceptible to MH as determined by the skinned single fibre caffeine test; also, cyclic AMP was increased in muscle from these patients. In earlier studies in pigs, cyclic AMP concentrations had been found to be increased immediately after slaughter [107], whereas adenylate cyclase concentrations had been similar in MH susceptible and control pigs [106]. Increased concentrations of cyclic AMP has also been reported in blood of MH susceptible patients after physical exercise [135]. None of these parameters, however, seem useful for diagnosis of MH susceptibility.

Adenylate deaminase deficiency

In individuals susceptible to MH, myoadenylate deaminase was either absent or less than one-third of the normal value more frequently than was found in non-susceptible persons [45]. However, the authors stated that the predictive value of this finding was too low for its use as a diagnostic test for MH.

Low weight proteins

Blanck and colleagues in 1984, suggested that two abnormal low weight proteins found in MH susceptible patients could be of assistance in diagnosing MH susceptibility [8]. Since then, these proteins have been found to be present in varying amounts in both normal and MH susceptible muscle [47, 143]. It has been suggested that the observed proteins are subunits of contaminating haemoglobin [47], a theory which has later been accepted by Blanck [7]. The conclusion, that electrophoretic separation of muscle proteins, at present, is not suitable for diagnosis of MH susceptibility, has been supported also by studies of Marjanen and Denborough [92] and Whistler, Isaacs and Badenhorst [144].

Calcium uptake by sarcoplasmic reticulum

Sarcoplasmic reticulum has been intensely studied in the search for the basic lesion of MH [37]. In one centre, determination of calcium uptake by the sarcoplasmic reticulum is used for the diagnosis of MH susceptibility [1, 2, 89, 90). MH susceptible muscle is found to have lower calcium uptake than normal muscle. In another study, 100% of children investigated with this method because of masseter muscle rigidity were found to be MH susceptible [131]. This is a much higher proportion than found in other centres, where approximately 50% of patients with masseter muscle rigidity are found to be susceptible [31, 49, 113, 127]. Also, the incidence of masseter spasm and hence MH susceptibility found in this study was several-fold higher than in other reports [14, 30, 79, 94, 108]. The validity of this test has therefore been questioned [32, 58, 140]. With different methods, calcium uptake has been found to be similar in susceptible and non-susceptible patients in one study [9], and lower in susceptible patients in another study [22]. Only recently has the "Boston test" [1, 2, 89, 90] been evaluated with identical technique in an independent laboratory [98]. In this latter study it was found that neither results of the standard contracture tests (halothane test and caffeine test) nor clinical episodes of MH correlated with the results of the calcium uptake test [98]. Therefore this test can not be recommended as a single diagnostic tool.

Intracellular ionized calcium concentration

In a recent publication, intracellular ionized calcium concentrations were described to be significantly higher in muscle biopsies from subjects susceptible to MH than in control biopsies [87]. The measurements were made with a calcium sensitive microelectrode on biopsies taken between 15 days and 4 months after a clinical episode of MH. Although these observations are very interesting, it cannot be excluded that the results were influenced by the circumstances of excision of the biopsies, for example the degree of stress, since the four MH patients had intercostal biopsies taken during local anaesthesia, whereas the three controls had general anaesthesia for thoracotomy [87]. The results are also in contrast to those obtained in lymphocytes by Klip and co-workers [80, 81], who found increased calcium only after exposure of the MH lymphocytes to halothane. However, since muscle is the primary tissue involved in MH, resting intracellular calcium concentrations could well be increased exclusively in MH muscle. Only when more results with the calcium microelectrode have been reported, and the results confirmed in other centres, can the method be further evaluated for diagnostic purposes.

Heat production

Heat production upon exposure to halothane was measured in muscle tissue with a microcalorimetric method [120]. It was found that heat production increased in both normal and

MH muscle, and there was no difference between the groups. At present therefore, this interesting method is not suitable for diagnosing MH susceptibility.

Nuclear magnetic resonance scanning

NMR scanning with phosphorus-31 has been used to demonstrate concentrations of high energy phosphate compounds and pH *in vivo* during exercise in subjects susceptible to MH [82, 93]. The preliminary results seem to indicate that concentrations of metabolites are fairly similar for susceptible and non-susceptible persons, but differences in time course of pH changes could be of informative value. Further studies utilizing this technique will probably clarify this point.

MUSCLE HISTOLOGY

Abnormalities of muscle histology are unspecific. They include internal nuclei, moth-eaten fibres and target or core-targetoid fibres, variations in fibre size, and signs of necrosis and regeneration [62, 67, 119, 121, 122, 134]. Sometimes signs of denervation are found [67, 121]. Changes are rarely seen in children, and the incidence of positive findings increases with increasing age of the patients [34]. Thus approximately 25–50 % of MH susceptible individuals can be expected to have one or more abnormalities [63, 119, 134]. It follows, that histology alone is insufficient for establishing MH susceptibility. However, it is still of major importance to perform muscle histology and histochemistry in order to rule out the presence of other myopathies.

CONTRACTURE TESTS

The most reliable method for diagnosis of susceptibility to MH is at present the *in vitro* contracture tests with halothane and (separately) caffeine. Similar results with these tests are obtained in many different laboratories all over the world. The basic principle of these tests is as follows: A piece of skeletal muscle, 10–20 mm long and 2–3 mm in diameter is suspended, immediately after excision, in a tissue bath with physiological Krebs solution at 37 °C and bubbled with 5 % carbon dioxide in oxygen. Viability is secured by recording the twitches elicited by supramaximal electrical stimulation. Initial length should be adjusted according to the evoked twitches and should be close to optimal length [85]. This is often obtained with a preload of 1–2 g in a specimen with the above dimensions. Tension is measured by a transducer and recorded before and after addition of a test drug. Mostly, a full dose–response curve with the test drug is obtained and the slope of this curve analysed. Because of variations in the ways these tests are performed and interpreted, it has been difficult to compare results of the tests between different MH units.

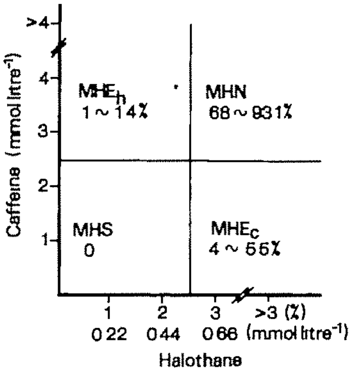

FIG. 1. Threshold concentrations of caffeine and halothane necessary for eliciting contracture (a sustained increase in tension of at least 0.2 g) in 73 normal control biopsies, obtained by the European MH Group. Diagnostic classification also shown. MHS = MH susceptible; MHN = MH non-susceptible; MHE = equivocal result.

In Europe, most centres performing these tests have agreed upon a common, standardized procedure describing in great detail how the tests should be performed [42, 43]. Each centre is encouraged also to obtain normal control biopsies following the same procedure. A halothane test and a caffeine test (*vide infra*) are included, and the parameter measured is the threshold drug concentration—that is, the lowest concentration of drug eliciting a sustained increase in basal tension of at least 0.2 g. Three diagnostic groups are recognized: MHS (susceptible) with abnormal results of both halothane and caffeine tests, MHN (non-susceptible) with normal results of both tests, and MHE (equivocal) with differing results (fig. 1). The MHE group has been created in order to minimize the risk of either false positive or false negative diagnosis. For the MHE patient, family studies will usually elucidate the true MH status.

The caffeine contracture test

The use of caffeine for diagnosis of MH susceptibility was introduced by Kalow and

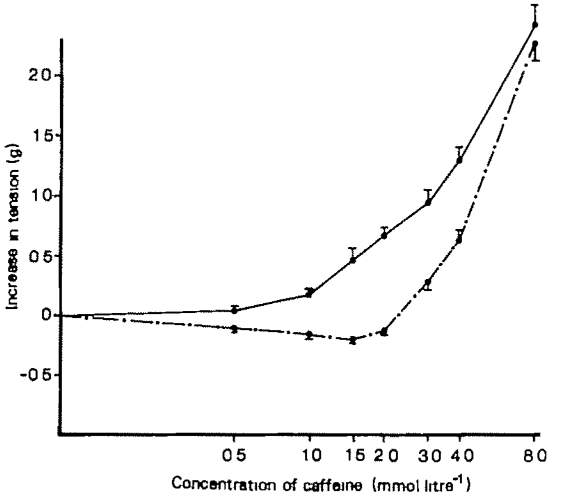

FIG. 2. Response to cumulative doses of caffeine in diagnostic muscle biopsies from 46 MH susceptible (——) and 54 non-susceptible patients (-·-·-). Mean ± 1 SEM. Statistically significant differences between groups for concentrations 0.5–2 mmol litre^{-1} ($P < 0.05$) (Redrawn from Ørding, Ranklev and Fletcher [113], with permission.)

colleagues in 1970 [74], and is now generally accepted as a reliable indicator of susceptibility, although problems with this test do exist in some MH units. The caffeine dose–response curve is shifted to the left in MH susceptible individuals compared with non-susceptible individuals (fig. 2). Originally, the caffeine test was performed at room temperature [73, 74], but now all MH units perform the test at 37 °C.

Criteria for susceptibility to MH vary between units, although generally it is the lower part of the dose–response curve which is used. As mentioned before, the European MH Group looks for the threshold concentration of caffeine eliciting a sustained increase in tension of at least 0.2 g [42, 43]. From analysis of results in normal control biopsies (fig. 1), a normal result of the caffeine test was found to be a caffeine threshold concentration greater than 2 mmol litre^{-1}. In other units, the concentration of caffeine producing a contracture of 1 g is found by interpolation and is called the caffeine specific concentration [10, 12, 19, 98, 105]. The normal values for this parameter vary markedly between units (table I). Other "dividing points" are also in use [6, 128, 139, 144]. In one centre, fraction of peak tension is calculated and the entire dose–response curve analysed [57].

Good control data with the caffeine test performed at 37 °C are scarce. Such biopsies should be excised under the same type of anaesthesia as the diagnostic biopsies and should be from the same muscle group. Only one test should be made on each specimen. Some published control data are shown in table I. Differing results are observed with the caffeine dose–response curve at crucial points: in some centres caffeine 2 mmol litre^{-1} never [19] or rarely [109, 128] induces contractures in normal muscle, whereas small contractures after caffeine 2 mmol litre^{-1} are regularly seen by others [57, 97]. This underlines the necessity of good control data obtained at the individual MH units.

Halothane contracture test

Halothane was introduced as a test drug by Ellis and colleagues in 1971 [36]. Normally, halothane alone produces significant contractures only in MH susceptible muscle, as shown in figure 3. However, in some normal specimens high concentrations of halothane (3–4 %) will elicit slight contractures (fig. 3). Halothane has been found reliable for establishment of MH susceptibility in many MH units and is widely used for this purpose. In a few centres, halothane contractures are not seen regularly and halothane accordingly is not used for testing by itself [12, 19].

Another difficulty with the halothane test is that the concentration of halothane in the tissue bath may vary substantially. It is not surprising that halothane, being a volatile anaesthetic with low

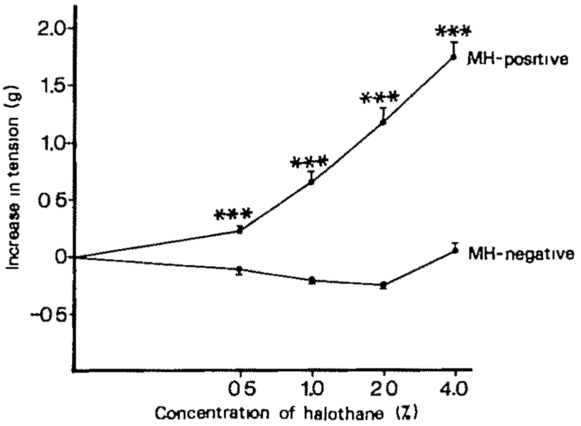

FIG. 3. Response to halothane in diagnostic muscle biopsies from 60 MH susceptible and 64 non-susceptible patients. Mean ± 1 SEM. Statistically significant differences between groups at all concentrations ($P < 0.001$). (Redrawn from Ørding, Ranklev and Fletcher [113], with permission.)

TABLE I. *Control data for caffeine test at 37 °C. CSC = Caffeine specific contracture (i.e. the concentration of caffeine eliciting a contracture of 1 g)*

Reference	Details
[12]	Vastus lateralis muscle. Anaesthesia with Innovar, diazepam, fentanyl and nitrous oxide. $n = 20$. CSC 5.5±0.63 mmol litre^{-1} (mean ± SEM).
[13]	Muscle and anaesthesia not specified for control patients. $n = 10$. CSC 7.53±3.48 mmol litre^{-1} (mean ± SEM). In all controls CSC $<$ 4.1 mmol litre^{-1}.
[19]	Muscle and anaesthesia not specified. $n = 29$. CSC $>$ 3.5 mmol litre^{-1} (range 3.5–10 mmol litre^{-1}).
[57]	Quadriceps muscle. Anaesthesia with potent inhalation agent in 30 patients; use of suxamethonium in 21 patients. $n = 33$. Caffeine threshold concentration 2–4 mmol litre^{-1}, CSC 2–4 mmol litre^{-1}, fraction of peak tension analysed.
[97]	Rectus abdominis. Anaesthesia: Thiopentone, nitrous oxide. Relaxation: pancuronium, tubocurarine, gallamine or suxamethonium. n not stated. Threshold for increase in tension 2–8 mmol litre^{-1}.
[99]	Rectus abdominis muscle. Anaesthesia not specified. n not specified. Response to caffeine 4 mmol litre^{-1} in 20 specimens 0.54±0.12 g (mean ± SEM).
[105]	Rectus abdominis muscle. Anaesthesia with thiopentone, fentanyl and diazepam. $n = 19$. CSC 4.85±2.1 mmol litre^{-1} (mean ± SEM).
[109]	Quadriceps, mostly vastus medialis muscle. Anaesthesia as used for diagnostic biopsies in individual units, mostly thiopentone–fentanyl–nitrous oxide or regional bupivacaine. $n = 73$. Threshold concentration for sustained increase in tension of 0.2 g $>$ 2 mmol litre^{-1} in 68 of 73 patients (fig. 1).
[128]	Quadriceps muscle. Anaesthesia not specified. $n = 15$ (three of whom required diagnostic muscle biopsy for reasons other than MH). Contracture $<$ 0.2 g at 2 mmol litre^{-1} in 13 of 15 patients, $\leqslant$ 0.4 g in all 15. CSC 7.92 ±4.48 mmol litre^{-1} (mean ± SD).
[134]	Vastus lateralis muscle. Extradural analgesia, agent not stated. $n = 8$. Threshold concentration for contracture $>$ 0.25 g: 3.56±1.16 mmol litre^{-1} (mean ± SD).

solubility in water, evaporates from the tissue bath. At a fixed vaporizer setting, therefore, the actual concentratrion of halothane in solution varies, depending on the shape and size of the bath, the flow of Krebs solution, gas flow and other factors. Hence it is necessary to measure halothane concentrations in the bath and adjust the vaporizer setting to obtain the desired concentration in the bath. The European MH Group in their procedure have specified the desired halothane concentrations, a step towards standardization in performance of the test. Instead of

2% halothane in the gas phase, they aim at halothane 0.44 mmol litre^{-1} in the Krebs solution.

Good control data with the halothane test have been obtained by the European MH Group [109] (quadriceps muscle, same anaesthetic technique for diagnostic and control biopsies). They found a small halothane contracture in one of 73 control subjects (fig. 1). The one control with halothane contracture reacted normally to caffeine and was not considered susceptible to MH. Gronert did not observe any contractures following 2% halothane in 33 controls (of whom 30 received halothane or enflurane for anaesthesia, and 21 suxamethonium) [57]. Britt and colleagues [12] saw a contracture of 0.1 g in one of 20 controls (quadriceps muscle, same anaesthetic technique for patients and controls). Moulds and Denborough [97] observed a small contracture in two of 18 control biopsies upon exposure to halothane (concentration not specified). In contrast, Nelson, Austin and Denborough [99] found that muscle from 18 of 57 normal controls developed contractures greater than 0.1 g with halothane in concentrations between 0.4 and 4% (rectus abdominis muscle, anaesthetic technique not specified). Rosenberg and Reed [128] observed contractures exceeding 0.1 g in three of 15 controls following 1% halothane (anaesthetic technique not specified, three of 15 controls having diagnostic biopsies for reasons other than MH). The observed discrepancies between the investigation units are most likely caused by a variety of factors: differences in halothane concentrations in the tissue baths, the excision of biopsies from different muscle groups and sometimes from patients with other neuromuscular disorders, the administration of a wide variety of drugs for anaesthesia. It is therefore mandatory for each laboratory to obtain its own control data.

A dynamic halothane test was described by Ellis and Harriman in 1973 [35]. In this test, the length of the muscle bundle is cyclically changed. The dynamic halothane test is incorporated in the European MH procedure [42], although not all units in the group are performing this test. Halothane contractures are greater in the dynamic test than in the static test [114], presumably as a result of enhanced calcium release following the stretching. Evaluation of the possible advantage of this test has been undertaken in two units, reaching different conclusions. Ranklev, Fletcher and Blomquist [118] found the dynamic test superior to the static test because 20% of their susceptible patients reacted to halothane only in the dynamic test, and would thus have been classified MH equivocal without the use of a dynamic test. Altogether, the diagnostic result (MHS, MHN, MHE) would have changed in 17% of their patients, if the dynamic halothane test had not been used [118]. In contrast, Ørding and Skovgaard [114] found that, by omitting the dynamic test, only three of 105 patients would have their diagnosis changed: two would be classified as MH equivocal instead of susceptible (in which case family studies would be undertaken), and one MH equivocal patient would be diagnosed non-susceptible. Since the single control biopsy with a halothane contracture reacted only in the dynamic test, Ørding and Skovgaard concluded that the dynamic test was not essential. More control biopsies in the individual units of the European MH Group, and further analysis of cases with previous unequivocal clinical episodes will probably clarify these discrepancies.

Factors with possible influence on contracture tests

Age of the patient (within a range of 7–83 yr) does not affect the result of the tests [57, 73, 112].

In one study, size of the individual muscle fascicles was found not to influence the magnitude of caffeine elicited contractures [12]. This is surprising, since the size of the contractures was simply measured in grams, as is the custom. The reason could be that the muscle bundles were fairly uniform in size. To circumvent the expected influence of different size of the muscle bundles and thus make results more comparable, the size of the contractures can be expressed as a percentage of either maximum tetanic tension or the contracture elicited by caffeine 32 mmol litre^{-1} [55, 57]. The latter parameter is more suitable for routine use, since it is obtained at the end of the test. If the specimen tears apart, as sometimes happens, it does not preclude the possibility of making a diagnosis.

In contrast to findings in animals, there is no correlation between muscle fibre type composition and magnitude of contractures or threshold concentrations in humans [45, 112]. This is presumably so because human muscles are of mixed type with a fairly uniform composition of the muscle groups studied, whereas animals have some muscles composed of a single muscle fibre type.

Composition of the Krebs solution, especially the calcium and magnesium concentrations, influence the magnitude of contractures and therefore have to be carefully controlled. Thus contracture responses to both halothane and caffeine are significantly decreased when the calcium concentration in the bath is decreased [25, 95, 101]. The contractures elicited by both halothane [48] and caffeine [113] seem to be weaker with increasing magnesium concentrations.

Temperature of the Krebs solution in the tissue bath influences the magnitude of the elicited contractures. Thus halothane elicited contractures in MH susceptible pig muscle at 37 °C, but not at 25 °C [100]. In human muscle, the caffeine contractures were reduced, when temperature was decreased from 37 °C to 25 °C [99], or 22 °C [12]. This does not seem to create problems now, since all centres are performing the contracture tests at 37 °C.

In pig muscle, it has been shown that deterioration of the muscle bundles used for the contracture tests increased sensitivity to halothane [50, 104]. Therefore, the time from excision of the biopsy to performance of the contracture tests should be as short as possible, and care should be taken not to damage the fibres during excision or preparation.

The caffeine used for the test should be pure caffeine base, since caffeine citrate or benzoate yield different results as a result of a shift in pH of the Krebs solution [65].

In one study, the contractures elicited by caffeine 4 mmol litre^{-1} were significantly larger when this dose was administered as a single bolus dose as compared with several cumulative doses [115]. This phenomenon could be the result of fatigue of the muscle tissue [17] or of tachyphylaxis. It illustrates the importance of standardized tests, if results are to be compared between different MH units.

Various drugs have been reported to interfere with the halothane and caffeine contracture tests:

Dantrolene has been shown to change the dose–response curve of caffeine in cat [26], rat [60], pig [5, 17] and human muscle, decreasing the caffeine contracture response [17, 102]. Dantrolene also blocks or attenuates the response to halothane in cat [26], pig [4], and human [6, 103] muscle. Conflicting results about the influence of *in vivo* dantrolene pretreatment on the contracture test results have been reported: one patient had dantrolene 100 mg in divided doses over 12 h before operation and still had abnormal results of the halothane and caffeine tests [124]. Another patient had dantrolene 100 mg four times a day for 2 days before operation and subsequently had a normal result of the caffeine test, whereas 1 year later without dantrolene pretreatment she had an abnormal result with the caffeine test [83]. In a third report, repeat contracture tests were performed with and without prior administration of dantrolene [117]. In four of five patients, the original abnormal results of the caffeine tests were changed to normal values after pretreatment with oral dantrolene for several days. The last patient received dantrolene 1 mg kg^{-1} i.v. immediately before anaesthesia, and continued to have an abnormal result with the caffeine test [117]. In susceptible pigs given i.v. dantrolene 3.5 mg kg^{-1} 15 min before the second biopsy, results of halothane and caffeine tests were not changed [104]. Thus, apparently, both dose of dantrolene and length of preoperative treatment influence the dantrolene effect. Accordingly, it seems wise not to administer dantrolene as prophylaxis against MH during anaesthesia for the diagnostic biopsy.

The calcium channel blocker verapamil changes the dose–response curve of caffeine and blocks halothane contractures in cat muscle [25], but was found in a study of MH susceptible pig muscle to potentiate some halothane induced contractures [51]. The calcium channel blocker diltiazem blocks or attenuates the halothane induced contractures in MH susceptible pig muscle [66], and changes the caffeine dose–response curve of human MH susceptible muscle [71] and cat muscle [20]. Procaine reduces the size of contractures elicited by caffeine in human muscle [97], but was reported not to inhibit halothane induced contractures in pig muscle [103]. The β-blocker propranolol has been found to attenuate the response to caffeine in susceptible human muscle without interfering with the response to halothane [110]. If possible, therefore, drugs should be discontinued before admission for diagnostic muscle biopsy. If this is not possible, the result of the contracture tests must be evaluated taking into account a possibility of drug interactions.

Other contracture tests

Halothane–caffeine contracture test. Halothane's potentiating effect on caffeine elicited contractures was first described by Kalow and colleagues in 1970 [74]. It is used in some American centres for diagnostic purposes [13, 105], but is found to be less accurate than the halothane or caffeine tests in other units [19, 98, 115, 128, 139]. Nelson, Flewellen and Gloyna [105] use the halothane–caffeine test to diagnose a third MH phenotype, the K-type, which they claim react to trigger agents differently from both susceptible and normal individuals. It is not yet settled if this group represents a true biological phenomenon or not. One of the disturbing points is that this phenotype is found in 10–20 % of control biopsies [125]. Another is that the K-type is only found in patients with very mild signs suggestive of possible MH, never in patients with unequivocal clinical episodes.

Halothane–suxamethonium contracture test. Fletcher and Rosenberg have described the *in vitro* effect of halothane in the presence of suxamethonium in patients *negative* to the standard tests for MH susceptibility (halothane and caffeine contracture tests) [46]. Muscle from patients with a history of masseter muscle rigidity developed halothane contractures, when suxamethonium was present, whereas muscle from patients without masseter muscle rigidity did not develop contracture. A new subgroup of patients was thus identified by clinical history and *in vitro* tests. They suggested that this subgroup of patients could be identical to the K-type patients described by Nelson, Flewellen and Gloyna [105]. Recently, this finding has been confirmed in a preliminary report from Nelson's group [76]. At present, however, the clinical implications of this finding are not known.

Caffeine–suxamethonium contracture test. Halsall and Ellis in 1979 described the combined use of caffeine and suxamethonium for diagnosis of MH susceptibility [59]. A graded contracture was seen in response to suxamethonium when this drug was added at the height of the caffeine elicited contracture. The authors speculated that this test could be of value in distinguishing between various possible MH phenotypes. However, Ørding and Skovgaard [115] did not obtain contractures with suxamethonium in this test and did not find it of any value for diagnostic purposes. Other groups apparently have not worked with this test.

Potassium chloride test. Moulds and Denborough in 1974 described the potassium chloride test for diagnosis of MH susceptibility [95]. They wanted to study the effect of complete depolarization of the sarcolemma, and obtained this by applying potassium chloride 80 mmol litre^{-1} to the surrounding medium. MH susceptible muscle was found to develop a marked contracture in response to potassium, whereas normal muscle did not. In order to increase the general diagnostic sensitivity of *in vitro* tests, the authors suggested the use of a battery of diagnostic tests instead of relying on one single test, and recommended the potassium test for this purpose. In a recent study of human muscle, agreement between the results of the conventional contracture tests (halothane and caffeine tests) and the potassium test was found in 75–80 % of subjects [115].

Suxamethonium test. This test was first introduced by Moulds and Denborough [95], who found MH susceptible muscle to develop contracture in response to suxamethonium 10 mg. In other laboratories suxamethonium induced contractures were not seen in the muscle preparations [46, 59, 115]. Later, Galloway and Denborough have shown that the responses to suxamethonium was evoked by the preservatives of the drug and not by suxamethonium itself [52].

Single, skinned muscle fibre tests

The method of skinning single muscle fibres, either chemically or mechanically so that they contain myofibrils and sarcoplasmic reticulum (SR) but no sarcolemma, has been described by Endo, Tanaka and Ogawa [39] and Wood [149]. As the *in vitro* contracture tests on whole muscle bundles are invasive and can be performed only on fresh tissue, the technique with single, skinned muscle fibres is attractive, since with this method a needle biopsy provides enough tissue. It is also possible to store the muscle tissue for some time before the tests are performed. The reaction of the single muscle fibres to calcium, caffeine and halothane is tested. Endo and colleagues [40] have found MH susceptible muscle more sensitive to calcium-induced calcium release from the SR than normal muscle. Both caffeine [38] and halothane [137] are considered to enhance calcium-induced calcium release, thereby eliciting contractures in MH susceptible muscle. The conventional contracture tests are not yet performed in Japan, so comparison of the skinned fibre tests with these tests has not been made in Japan. Wood and co-workers [149, 150] developed a caffeine contracture test on single fibres. This test has been evaluated by Britt and colleagues in a large series of patients [13]. They found it a useful test, although some overlap in results were seen between diagnostic groups. Unfortunately, the diagnosis in this unit is based primarily on the combined halothane–caffeine test, which is found less discriminative in other units. The skinned fibre tests therefore need further evaluation of diagnostic sensitivity and specificity.

CONCLUSION

Of all the tests which have been suggested for diagnosis of susceptibility to MH, only the invasive and cumbersome halothane and caffeine contracture tests have been proved reliable. Even with these tests, control data of good quality are scarce. Research for a reliable non-invasive test is continued. However, it is possible that a definitive test cannot be developed until the exact molecular defects causing MH are found. Until this occurs, a non-invasive test which could be used in the selection of patients for muscle biopsy would be of great help. At present, NMR spectroscopy or the lymphocyte quin 2 test seem promising for this purpose, but both need further evaluation. Until a new definitive test has been developed and properly evaluated, it would be of benefit to standardize as much as possible the contracture tests in use. Both a halothane and a caffeine test should be included, as is the case in the procedure agreed upon by the European MH Group [42, 43].

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MALIGNANT HYPERTHERMIA: RELATIONSHIP TO OTHER DISEASES

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The vast majority of patients identified as carrying the MH gene, do not appear to have any other associated disease. There is, however, a small and apparently increasing number of patients in whom the MH trait is reported to be associated with a second disease within the same individual. When these associations are reported the assumption is made, rightly or wrongly, that having one of these diseases predisposes that individual to MH if exposed to the appropriate triggers.

In this paper I explore the relationship between MH and these other diseases and attempt to identify those disease associations which may be significant. For each association I discuss, I shall assign it to one of two catergories: what I believe to be significant associations, and associations that seem only to be chance occurrences. It is not my aim to review and enumerate the entire literature relating to this topic.

Problems associated with the task

When one begins a task such as this, several problems immediately become apparent. First, a decision has to be made on criteria that must exist before one will accept that MH has in fact occurred. Second, if there has not been a clinical MH reaction, what evidence is there that the MH gene exists in a particular individual? Third, the diagnostic criteria for the proposed associated disease must be defined.

What, then, are the diagnostic criteria for one to accept the diagnosis of clinical MH? Will there need to be evidence that the patient had classical, full blown, clinical MH, supported by all the appropriately documented laboratory test abnormalities that are known to occur in such cases?

If these are the criteria that must exist before one would be willing to accept the diagnosis of MH in case reports, and by implication that the MH gene exists in that individual, then almost all of the case reports that purport to document disease associations with MH would have to be ignored. In the older literature, where full blown clinical descriptions were more likely to be reported, rarely were the supportive diagnostic laboratory tests carried out, since MH was often a retrospective diagnosis. In the more recent case reports the full blown clinical picture is almost never reported, because of the much greater index of clinical suspicion for MH amongst anaesthetists; also, definitive therapy would normally be instituted as soon as there is any clinical suspicion of the disease.

Fortunately there is a way out of the dilemma of trying to determine if MH has occurred, through the use of diagnostic tests for MH. If diagnostic tests for MH are undertaken in a person who had a clinical reaction suggestive of MH, and if they are abnormal, then one is on firm grounds in concluding that (1) the gene for MH exists within that particular individual and (2) the clinical episode was MH (even though the clinical features might have been very incomplete and the appropriate diagnostic laboratory studies missing).

If the presence of a specific test result is to be accepted as proof that the MH gene exists within an individual, one is obliged to evaluate the testing that has been proposed to be able to identify MH susceptibility, and in particular to consider its sensitivity and specificity. While there is general agreement that *in vitro* contracture tests carried out on biopsied skeletal muscle are reliable for identifying the MH trait, there still remains considerable variability in the interpretation of the results—that is what test response can actually be considered an abnormal response. Although these issues are far from being completely settled yet, considerable progress has been made in this area since the introduction of the first

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contracture test in 1970 by Kalow and colleagues [17]. To date the European MH Group has made the greatest strides in developing standardization of test procedures and interpretation of test responses [10].

Tests other than *in vitro* contracture tests are also reported, by certain laboratories, to be able to distinguish MH-susceptible from normal individuals. Contracture tests carried out on skinned single fibres [39], sarcoplasmic reticulum calcium uptake [25] and platelet nucleotide assay [38] are examples of such tests. Attempts by other laboratories to validate the reliability of these tests either have not be reported or have been unsuccessful [27, 33]. Therefore, until there is more universal agreeement on the validity of these tests, other than *in vitro* contracture tests, to "prove" the presence of the MH gene, when any of these tests are the only ones that have been used to identify or confirm MH susceptibility, there may be hesitation in accepting the conclusion that these individuals actually are at risk for MH.

Is the association significant?

In attempting to assess whether or not a reported co-occurrence of two different diseases is significant, there are several items that have to be considered. First, if one has reliable data describing the prevalence of the diseases in question and if both are rare diseases, intuitively, one thinks that the association may be significant. On the other hand, if one of the diseases has a relatively high prevalence within the population, then observations on much larger numbers of persons would be necessary before one would readily accept the association as anything more than chance. Unfortunately, there are no good data describing the MH gene frequency within the general population. What we do have are data on the frequency with which clinical MH episodes occur during general anaesthesia within various population groups [31]. Unfortunately this type of information is not nearly as useful as knowing what the actual gene frequency is when trying to assess the significance of postulated disease associations.

A second approach to assessing the significance of a reported disease association is to begin by reviewing the disordered mechanism in the one disease and then looking at the other disease to determine if there is any likelihood of a similarly disturbed mechanism in it. If a similarity in disturbed mechanism appears to exist, one will be more apt to conclude that the disease associations have significance. If there does not seem to be any similarity in their disordered mechanism (either known or proposed), then there will be the tendency to regard these reports as nothing more than chance associations or at least unproven beyond reasonable doubt. Unfortunately, this approach is quite limited because the disordered mechanism(s) is/are not fully worked out in MH and certainly not in most of the diseases for which an association has been proposed.

The third approach is one that analyses the disease associations in terms of the end-organ that is known to be primarily affected. In the case of MH the end organ is skeletal muscle.

THE ASSOCIATIONS

All of the diseases that I categorize as appearing to be related (groups (1) and (2) in table I) fall into the broad general classification of myopathies. Since they all share, along with MH, the common property of having skeletal muscle as the defective end-organ, it is intellectually satisfying to speculate that they may indeed share some common disordered mechanism(s) which could allow them to have a significant inter-relationship. There is no such homogeneity within the other group of diseases and, as a result, it is difficult to hypothesize how they might share a common disordered mechanism of disease with MH and, therefore, how they might relate to each other in a significant way. Consequently I have decided to characterize diseases assigned to this group as nothing more than chance occurrences.

Diseases which appear almost certainly to be related

Central Core Disease (*CCD*). CCD is a morphologically distinct myopathy with quite variable clinical features. Thus patients may range from being asymptomatic to severely disabled as a result of muscle weakness. Diagnosis depends upon the demonstration of "cores" in a significant number of muscle fibres, using oxidative enzyme histochemistry applied to fresh frozen sections of biopsied skeletal muscle. Autosomal dominant inheritance is observed in most subjects [37].

The association of this, apparently rare, myopathy with MH was first reported by Denborough, Dennett and Anderson in 1973 [5]. Subsequently, others have also noted the association. In all

TABLE I. *Diseases which have been reported to be associated with MH*

(1) Diseases which appear almost certainly to be related
    Central core disease
(2) Diseases which appear possibly to be related
    Duchenne muscular dystrophy
    King–Denborough syndrome
    Myoadenylate deaminase deficiency
    Other myopathies, for example the Schwartz–Jampel syndrome, the Fukuyama type of congenital muscular dystrophy, Becker muscular dystrophy, periodic paralysis, myotonia congenita, the sarcoplasmic reticulum adenosine triphosphatase deficiency syndrome and mitochondrial myopathy.
(3) Diseases in which the association appears coincidental
    Sudden infant death syndrome
    Neuroleptic malignant syndrome
    Other diseases, for example lymphomas, osteogenesis imperfecta and glycogen storage disease.

patients with CCD in whom *in vitro* contracture tests have been carried out, with one exception (commented on by Harriman [15]), the results have been abnormal, indicating that the two conditions co-exist. To date, we have found the co-existence of MH and CCD in 11 patients [37]. In this group of patients there is very good correlation between the results of *in vitro* contracture tests and the clinical occurrence of MH, thus indicating that the abnormal test response is specific for MH. For example, in the 11 patients we have personally observed who have abnormal contracture responses, two of them have had MH reactions during general anaesthesia and a third developed masseter rigidity following the injection of suxamethonium.

Thus on the basis of the presently available evidence, all patients with CCD must be considered at risk from MH unless *in vitro* contracture tests indicate otherwise. This is the only disease association where there is such a tight correlation with MH.

Diseases which appear possibly to be related

In this group of diseases, with the exception of the reports of MH associated with Duchenne Muscular Dystrophy (DMD) and the King–Denborough syndrome, the reports are often fragmentary and incomplete, making it difficult to conclude if there is a relationship or not. They are mentioned more to raise the possibility that the association does exist and to alert those involved with patients afflicted with these rare diseases to look at them very closely during general anaesthesia and to encourage the reporting of any unusual anaesthetic occurrences.

Duchenne Muscular Dystrophy (*DMD*). DMD, an X-linked muscular dystrophy, is the commonest myopathy affecting children, even though it only affects males. Although there were suggestions that MH occurred in patients with DMD [23, 35], the first reports of abnormal *in vitro* contracture responses being used to reinforce a suspected clinical diagnosis of MH were published in 1982 [30] and 1983 [2]. The risk for MH in patients with DMD is unknown and the relationship is not similar to that described for CCD. In the family of the male child reported by Brownell, Fowlow and Paasuke [1], investigation of other family members proved that the traits for DMD and MH were independent. Although there are now several cases of DMD and MH reported in the same patients, the results of family investigations are inadequate to determine whether the traits are occurring independently, as was the case in our family, or whether there may be a closer relationship in some pedigrees. Until such information is available, I recommend that the two traits be considered independent and thus family members who are free of the DMD trait cannot be advised that they are free of the MH gene unless definitive *in vitro* contracture testing has been carried out.

King–Denborough Syndrome. This syndrome was first reported after a review of cases of MH in Australia and New Zealand by King and Denborough in 1973 [20]. Subsequently it was labelled the King–Denborough syndrome by McPherson and Taylor [26] when they reported a further case and reviewed the literature. The syndrome as originally described was characterized by short stature, slowly progressive myopathy, thoracic kyphosis, lumbar lordosis, undescended testes, pectus carinatum, and an unusual facial appearance characterized by a small chin, low set ears and antimongoloid obliquity of the palpebral fissures. Unfortunately there were no laboratory features that distinguished the children with certainty. This appears also to have been so with the other reported cases, thus making it difficult to identify these patients with any degree of certainty. The muscle pathology is only briefly referred to in the reports and it is not clear if special studies such as enzyme histochemistry and electronmicroscopy were carried out to rule out a morphologically distinct myopathy such as CCD.

Certainly, the phenotype as described for the King–Denborough syndrome could be seen in patients with CCD.

Myoadenylate Deaminase Deficiency (MDD) Absence of myoadenylate deaminase activity was first described in five of 250 human muscle biopsies by Fishbein, Armbrustmacher and Griffin [11]. Four of the patients with absent enzyme activity reported a degree of exercise intolerance manifested as muscle cramps, stiffness or soreness. Subsequently Kelemen and others [19] reported that MDD appeared to relate to a clinical syndrome of exertional myalgia, and in one family there was a suggestion of autosomal dominant inheritance.

Fishbein and colleagues [12] reported the results of a study that evaluated the hypothesis that there was an association between MH and MDD. Within their total group of patients was one family in which five members were studied. In this family the gene for MH appeared to be inherited from the paternal side, while the gene for MDD appeared to be inherited through the maternal side. This finding suggests that the association of the two diseases is nothing more than coincidental and similar to what was found in the pedigree where DMD and MH co-existed [2]. Although the exact frequency of the MDD gene in the population is unknown it appears to be quite common [11, 19]; thus it should not be surprising that the two diseases would occur together.

Other myopathies. There are several case reports in the literature where the conclusion has been reached that MH is associated with some other well defined myopathies. In some instances the association has been reported on the basis of clinical findings alone and in other instances on the basis of the outcomes of *in vitro* contracture tests. In none of them are there reports of both types of information, as has been the case with CCD and DMD.

The diseases listed here include the Schwartz–Jampel syndrome [36], the Fukuyama type of congenital muscular dystrophy [28], Becker muscular dystrophy [16], periodic paralysis (Brownell, unpublished observations), myotonia congenita [13], the sarcoplasmic reticulum adenosine triphosphatase deficiency syndrome [18] and a mitochondrial myopathy [29]. Much more extensive documentation of the anaesthetic experiences of this group of patients will have to become available before we will be able to state, with certainty, whether MH has in fact occurred in some of the patients and what proportion of patients are actually affected, and, through the study of pedigrees, to determine whether or not the diseases just co-exist.

Diseases in which the association appears coincidental

Sudden Infant Death Syndrome (SIDS). SIDS is the most common diagnosis in infants who die at 1 month to 1 year of age [40]. Attention was first drawn to its association with MH by Denborough [3], in the father of a child who had died of SIDS. Subsequently Denborough, Galloway and Hopkinson [6] reported that contracture responses were diagnostic for MH in five of 15 parents tested who had children die from SIDS. The documentation of abnormal anaesthetic events in this group of patients has been fragmentary. Ellis and Heffron [9] were not able to confirm the high frequency of the association that had been reported by Denborough, Galloway and Hopkinson [6]. Ellis and Heffron [9] concluded that their data, demonstrating six separate episodes of SIDS in 147 known MH susceptible families, was not significantly different from the reported incidence of two to eight episodes occurring per 1000 live births. Although we have not investigated nearly as many pedigrees in our unit in Calgary as either Denborough or Ellis, our experience would agree with Ellis' conclusion, since we have only recorded one instance of SIDS in our MH patient population.

Neuroleptic Malignant Syndrome (NMS). NMS is characterized by hyperthermia, hypertonicity of skeletal muscles and fluctuating consciousness, along with instability of the autonomic nervous system in a patient taking antipsychotic agents such as phenothiazines, butyrophenones and thioxanthines. The creatine kinase concentration is often markedly increased [14]. Because of the similarity of some of the clinical features of NMS and MH, it is not surprising that there should have been speculation that the NMS might somehow be related to MH. A very limited number of studies have been made in patients to try and answer the question as to whether or not there is an association. The case report of Lotstra, Linkowski and Mendlewicz [24] indicated that general anaesthesia consisting of thiopentone and suxamethonium, for electroshock treatment, was given safely on numerous occasions to a patient who had previously had the syndrome. The patients reported by Denborough, Collins and Hopkinson [4] and Downey and colleagues [7] had abnormal *in vitro* contracture responses that are typical for individuals with the gene for MH. On the other hand, not all patients with NMS show abnormalities when they are evaluated with contracture tests, as is shown by the reports of Scarlett, Zimmerman and Berkovic [34], Tollefson [41] and Krivosic-Horber and colleagues [21] who, in total, reported eight negative *in vitro* contracture studies in patients who had previously been diagnosed as having had NMS.

The postulated disturbed mechanisms in NMS are felt to be in the CNS and the muscular activity is assumed to be secondary to the CNS abnormality. Thus it is difficult to envisage how these two diseases, with entirely different disordered mechanisms, could be closely related.

Other diseases. This list is quite brief and, as outlined in table I, includes Burkett's lymphoma [22, 42], osteogenesis imperfecta [32] and a biochemically uncharacterized glycogen storage disease [8]. In each instance it is possible to conclude that something other than MH might have happened which would equally well explain the clinical problem. In additon, for none of these patients was there confirmation, through the use of diagnostic tests, that the MH trait was in fact present.

IMPORTANT FUTURE ISSUES

Until the frequency of the MH gene within the population is known, interpreting the significance of proposed disease associations will continue to be problematic. Except for CCD, where the evidence suggesting a significant relationship with MH seems indisputable, I believe that it might be possible to account for every other disease association reported to date by chance. For such a conclusion to be valid, one would have to assume a fairly frequent occurrence of the MH gene within the population at large. The apparently higher incidence of MH within the total group of patients with myopathies could be explained if the MH gene was to be located in close proximity to the genes for the various myopathies. Of course, proof for such an hypothesis awaits identification of the various loci for the diseases under consideration.

Today, the presence of the MH gene within an individual can only be determined if a clinical MH reaction has occurred or if some other type of diagnostic testing has been carried out. Since neither of these identification techniques would ever be useful for determining the MH gene frequency within the population, it seems certain that it will be sometime in the future before definitive information will become available to resolve many of these problems. The development of a probe for the MH gene or a simpler diagnostic test for MH that would be suitable for mass screening of the population would provide the means whereby this information could be obtained. In the meantime, it is necessary to stress the importance of carrying out detailed family studies, using a combination of clinical, morphological (including histochemistry and electronmicroscopy) and contracture studies, in all pedigrees where associations between MH and other diseases occur. Using these techniques, even though they are somewhat cumbersome, it is possible to decide just how much significance to attach to the various disease associations with MH that have been reported, provided that a sufficient number of patients and their families are studied in appropriate detail. There is no doubt the number of reports of new associations will continue to increase in the future, so we must be prepared to work diligently toward trying to resolve their significance, even though the tools for doing this are less than optimal.

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MALIGNANT HYPERTHERMIA MYOPATHY—A CRITICAL REVIEW

D. G. F. HARRIMAN

When malignant hyperthermia (malignant hyperpyrexia, MH) was first recognized, clinical observation suggested that the disorder must reside in skeletal muscle itself: the production of spasm by the relaxant suxamethonium, the frequent discovery of generalized muscle rigidity during a major MH reaction and the accidental finding that a tourniquet applied for surgery protected the limb from rigidity during an MH crisis.

An origin in muscle was also supported by Isaacs and Barlow [24] who showed that some members of a known MH family had significantly increased serum concentrations of creatine kinase and could logically be regarded as the MH susceptible members. Although CK concentrations were later shown to be unreliable indicators of susceptibility, this observation was of crucial importance in placing MH among the myopathies. The consequence was that muscle biopsies were made on MH patients to investigate the muscle disorder and to devise reliable *in vitro* tests of susceptibility.

It was expected at that time that muscle biopsy of all susceptible patients would show a myopathy which would be a primary structural one, responsible for the abnormality of function that produced the MH crisis. The writer held this conventional view in 1973, but it became difficult to account for an increasingly large proportion of patients, especially young ones who were MH susceptible on *in vitro* testing but whose biopsies were completely normal morphologically. Belief in the primary nature of a structural myopathy that was only found in a minority of susceptible patients was finally abandoned in 1978.

This paper is a review of the published accounts of muscle histopathology in patients ostensibly susceptible to MH, and interpreted as MH myopathy or neuropathy by their authors. The rare associations of MH with other genetic myopathies and post-MH rhabdomyolysis are referred to only when relevant to the discussion of MH myopathy. The decriptions of the myopathy are remarkably varied, possibly the result of uncertainties of histological interpretation and the almost universal absence of *in vitro* tests for the diagnosis of MH susceptibility.

The review will be compared with a summary of the histology of 1400 biopsies made in the Leeds Malignant Hyperpyrexia Investigation Unit [7] which allows MH myopathy to be redefined.

The term *MH myopathy* may be defined as the histopathology present in a proportion of MH susceptible patients and thought to be directly related to MH. It is not used for muscle reactions to coincidental disease, or for the rare association of MH with another genetic myopathy. True MH myopathy appears to be more frequent in pre-anaesthetic MH than in post crisis MH, but opportunities to examine muscle then are fewer. In addition, major crises are liable to be complicated by extensive muscle necrosis (rhabdomyolysis) which will obliterate the signs of MH myopathy that may have developed previously in its territory. There seem to be several mechanisms initiating rhabdomyolysis, but it is not a component of MH myopathy. As is well known, it is liable to occur in the severe MH crisis, producing myoglobinuria and renal failure, but may result from heatstroke [33], drugs causing heatstroke [6] and from prolonged rigidity without hyperthermia [40], among lesser known causes.

MH myopathy in the literature

Families in which a proband had suffered a severe or fatal episode of MH were now subjected to muscle biopsy. The first report to make an impression was that of Steers, Tallack and Thompson [41], which had a curious conse-

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quence. On examining the father of their MH patient, they found wasting in the legs, with focal hypertrophy in the thighs (it is now known that focal hypertrophy does occur in MH myopathy, but is very rare). The muscle showed segmental necrosis, regeneration, size variation including some very large fibres and some internal nuclei. The authors were reminded of Barnes' myopathy, not widely known at the time. Barnes had described something similar in a very large kindred, and presented it in his Presidential address to the Royal Society of Medicine in 1932 [1]. A postscript occurred in 1973 when a distinguished physician who had one of Barnes' surviving patients under his care invited D. W. Sumner and the writer to see the patient. The examination strongly suggested Charcot Marie Tooth disease, and a similar diagnosis was arrived at by D. Riddoch (personal communication) in two other surviving members of the kindred.

The myopathy described by Steers and his colleagues was almost certainly MH myopathy.

From 1971 to 1975 Reske-Nielsen and her colleagues [32, 36–38] presented a number of papers describing their findings in two MH families. The proband in the first family was a 13-yr-old boy who was thought to have suffered an MH reaction, his temperature increasing to 38.2 °C. Biopsies were obtained from the proband (tibialis anterior), and from his mother, sister and brother (palmaris longus in all three). All showed collateral re-innervation. (This means re-innervation of the muscle fibres of a recently denervated motor unit by sprouts emanating from the subterminal nerves of a neighbouring unit. The axonal branching results in a single subterminal fibre supplying many endplates instead of the normal one or two.) Collateral reinnervation is an extremely sensitive indicator of neurogenic disease, but in the absence of the classical signs of denervation such as type grouping and large group atrophy, it means only that denervation has occurred and then been compensated. Ultrastructural studies in this first family showed severe contraction artefact.

The second family, a kinship of 147, contained two probands, both of whom had died of MH. Biopsies were obtained from 12 healthy members; the muscle tissue showed minimal change only, but 11 out of 12, all from the palmaris longus, showed collateral re-innervation. There were two relevant features on electron microscopy: Z-line streaming and a few tubular aggregates.

There are several reasons why collateral re-innervation *per se* should not immediately be accepted as evidence of a neuropathic element in MH. The palmaris longus is a muscle which varies greatly in size and is sometimes absent—it has no useful function and is undergoing involution. It is not known whether this process could induce collateral re-innervation. Considering that the evidence for denervation in these two families was for denervation followed by re-innervation only, and the doubtful evidence of MH susceptibility, the concept of neurogenic disease as a basis for MH is not fully supported. It may be added that, in the writer's series, the motor innervation was examined several hundred times in a different muscle, the vastus medialis, and was never abnormal in MH susceptible patients.

In 1973 the Malignant Hyperpyrexia Investigation Unit, formed 2 years previously in Leeds, published its first results of histology in MH susceptible and insusceptible subjects [19]. The investigations required open motor point muscle biopsy for both *in vitro* tests and histology. The tests provided reliable diagnosis of susceptible and insusceptible patients and could then be correlated with the histology. The results obtained in the first five families were published [19]. At that time it was assumed that any abnormalities present in MH suceptible patients would be components of MH myopathy, but even then some results showing normal muscle in MH susceptible subjects were puzzling. Some biopsies did show moth-eaten fibres and increased numbers of fibres with internal nuclei, later to be accepted into the cadre of MH myopathy, but many other abnormalities seen first in MH susceptible patients were later found to have been incorrectly attributed to MH myopathy. To give an example the impressive "spotted" or "lobulated" fibres in which mitochondria, glycogen and sarcoplasmic reticulum formed clumps within the fibre were seen in abundance in the third patient investigated and seemed to merit a place in the histopathology of MH myopathy. One thousand biopsies later the same pattern of spotted fibres had been seen in six MH susceptible patients and in six insusceptible patients, thus preventing attribution to MH myopathy either specifically or characteristically.

In three papers [25, 26, 21], a neurogenic basis for MH was again proposed. In the first, six members of two known MH families showed type grouping. This occurs as a result of collateral re-innervation, when a motor unit composed of one type of fibre re-innervates a neighbouring, recently denervated unit consisting of fibres of the other main type. The re-innervating nerves convert the recently denervated muscle fibres to their own type and in that way large groups of uniform fibre type can be formed. Type grouping at that time was diagnosed by some authors on the slight basis of small groups of 10–15 fibres, but it is now known from necropsy studies that such small groups occur in normal muscle. For single groups to be considered diagnostic of denervation, around 100 fibres are required. In practice, type grouping is quite rare and is only persuasive when several large groups impinge. The illustrations in the first paper mentioned [25] illustrate a rather small group, and another smaller one is described as "early" type grouping.

The second Isaacs paper [26] also claimed that MH had a neuropathic basis. Two subjects, aged 54 and 18 yr, from a known MH family showed group atrophy. Like type grouping, atrophied fibres signify denervation only when present in large groups; the atrophied fibres are then unmistakably denervated. Small groups may be myopathic or denervated and, if only small groups are present, then neurogenic atrophy cannot be diagnosed with confidence. The illustration is of a small group of particularly small fibres, some possibly being fibre fragments.

The third report [21], on four patients with increased CK concentrations, again proposed a neuropathy on the basis of small group atrophy, along with swelling of mitochondria and single atrophied fibres.

It has to be said that these three papers and previous ones have not made a convincing case for neurogenic disease, but they were written 10 or more years ago, since when diagnostic criteria have been modified.

In 1977 Britt, Kwong and Endrenyi [5] mentioned their findings in MH myopathy in the course of a review of Malignant Hyperthermia management. They stated that 20% of probands had normal muscle, but others showed internal nuclei, targetoids (identical with cores), fibre size variation with some tiny fibres and, on electron microscopy of a core, undoubted Z-line streaming. These findings, in patients whose susceptibility to MH was determined by reliable *in vitro* tests, are close to those of the Leeds MH Investigation Unit, especially the description of cores and internal nuclei.

Gullotta and his colleagues made a significant contribution to MH myopathy in the period 1975–83 [11–14]. Gullotta regretted that *in vitro* testing was not available to him, but considered that a severe episode of MH and especially a fatal one could be a reliable indicator. His earliest paper [12] reported histopathology in four patients: one died from MH (muscle tissue removed immediately after death) two were MH survivors, and one patient was considered susceptible. The findings in all indicated a pre-existent myopathy, with fibre necrosis, internal nuclei, one core and, on electron microscopy, dilated cisterns and convoluted rolls of sarcolemma.

Two papers by this group [11, 14] described proliferation of tubules (tubular aggregates) in a 24-yr-old chronic alcoholic who developed MH. The Leeds biopsies include a small number with tubular aggregates in asymptomatic patients, both MH susceptible and insusceptible, and therefore not diagnostic of MH myopathy.

The 1983 paper of Gullotta and Spiesz-Kiefer [13] was the most important, based on a series of 41 muscle biopsies on MH susceptible patients and some relatives. Twenty biopsies were normal; two showed rhabdomyolysis; two central core disease: one contained cores and moth-eaten fibres and another tubular aggregates. Children were usually normal, and the remaining patients showed minimal changes.

Gullotta's findings are similar to the writer's in demonstrating a fairly high proportion of normal biopsies, a significant association of MH and Central Core Disease, the rarity of histopathology in children and some features of MH myopathy in common (internal nuclei, cores and moth-eaten fibres).

There followed a case report [39] which was assumed to show that MH myopathy was a neuromyopathy. The patient concerned was a 31-yr-old male with big muscles, who exhibited proximal weakness of the upper limbs. During anaesthesia the CK concentration increased to 6120 units (normal range 35–175 units) and the rectal temperature to 39.4 °C, at which point anaesthesia was discontinued. Recovery took place over a number of days. The surgery was dental and there is no note of suxamethonium having been used. A muscle biopsy was briefly reported as showing "typically neurogenic" features of type grouping and a target fibre. The illustration can only muster 16 fibres of the same type and the target fibre shown differs in no way from a core.

In 1980–1982 two papers appeared from Japan. The first [42], reported two patients whose muscle was examined by using skinned muscle fibres for *in vitro* tests. In the first, a male of 30 yr, all skinned fibres contracted on testing, and the biopsy showed mild size variation, necrosis, internal nuclei and moth-eaten fibres. This must qualify as MH myopathy. The second patient was a male aged 42 yr, whose small groups of atrophied fibres suggested a neuropathic process.

Two years later another report from Japan [34] used extensive examination of muscle at postmortem to try to confirm whether a patient had died of MH. The patient was a male aged 65 yr who had died in a hyperthermic crisis with rigidity. The temperature increased to 42 °C during an operation for clipping of an anterior communicating aneurysm. This bled into the anterior hypothalamus, wherein lies the temperature regulating centre. The muscles showed no certain evidence of MH myopathy. The questions posed by this most unusual case could only be answered by investigating the patient's siblings or children for MH susceptibility.

Histopathology of stress-susceptible porcine muscle

Very little has been published on the possibility of MH myopathy in swine. In 1977 Palmer, Topel and Christian [35] described their findings in MH susceptible pigs. Contraction artefact in the form of supercontracted fibres was more prominent in the susceptible than in control animals. One muscle, the longissimus, contained more fibres with internal nuclei than other muscles sampled. In another investigation Venables [43] found that the only clear morphological abnormality was supercontraction.

Independent myopathies sometimes associated with the MH trait

From time to time reports have been published linking MH with various myopathies, of which undoubtedly the most frequently associated is central core disease [8–10, 17]. The majority of patients with central core disease so far tested have been shown to be MH susceptible, and investigation of their families is always advisable. Association of MH with other myopathies appears to be rare so far, but single cases continue to be reported with and without *in vitro* tests. In the following account an independent myopathy was associated with MH, but reported initially as a distinct form of MH myopathy.

In 1973 King and Denborough [29] gave an account of four unrelated boys all of whom had suffered from a severe episode of MH, three of them fatal. They all showed distinctive dysmorphic features, including antimongoloid obliquity of the palpebral fissures, pectus carinatum, low set ears, mandibular hypoplasia, cryptorchidism, kyphosis and short stature. Such a child presenting for surgery would alert the anaesthetist to the possibility of MH. (The appearances are well shown by Bergeson and co-workers [2].) Several other children with the King syndrome have also suffered MH reactions. A muscle biopsy was performed on one of these, a 7-yr-old boy [27]. It showed an undoubted congenital myopathy of uniform fibre type with marked fibre size variation. Other authors have remarked on the similarity of King's syndrome to that of Noonan: both share similar dysmorphysms. Noonan's syndrome is by far the more common [30]. Hunter and Pinsky [23] studied 27 children with Noonan's syndrome in whom there had been a total of 25 general anaesthetics, but no instance of MH. Until *in vitro* studies have been made on the families concerned it may be best to combine the two syndromes into one, assuming a rare or infrequent association with MH.

Malignant hyperthermia—post hoc

Biopsies are often taken during or after MH crises in the expectation that MH myopathy will be shown but, as already stated, the more severe episodes of MH may cause rhabdomyolysis and obliterate pre-existing MH myopathy. Now and again rhabdomyolysis is itself incorrectly interpreted as MH myopathy.

Hausman [20] studied at postmortem the muscles of a male of 22 yr who had died of MH. He found not only rhabdomyolysis, but an unusually larger number of large rounded hyaline fibres. These are a common form of artefact resembling supercontracted fibres and are often present in excess in irritable muscle.

Bernhardt and Schiller [3] described the muscle specimens obtained from two patients, one a biopsy taken 3 months after an MH episode, and the other at postmortem after a fatal episode. The authors considered that their findings, while not specific, gave evidence of a primary myopathy. The postmortem muscle showed changes like those of myotonia congenita and the biopsy suggested myositis. Myotonia congenita was suspected because there were rows of internal nuclei, yet these occur rarely in that disorder but are a feature of MH myopathy. The diagnosis of "myositis" in the post-MH biopsy is more difficult to explain, but could refer to a regenerative and histiocytic reaction to rhabdomyolysis. Such a reaction could well be active 3 months after the MH episode, provided the areas of muscle necrosis had been extensive. Thus there is reasonable evidence of MH myopathy in the first, but not the second, of the two cases reported.

Schmitt and co-workers [40] described the case of a 5-month-old male infant who developed extreme generalized muscle rigidity immediately after induction with halothane, nitrous oxide–oxygen and suxamethonium, but without significant increase in temperature. The baby died and a lumbosacral meningomyelocoele was confirmed. The authors wondered whether this could be a *forme fruste* of MH resulting from failure of heat regulation in infancy. In such a case *in vitro* tests on the parents and family would be necessary to provide an answer. It was of some interest that, histologically, the muscles showed severe rhabdomyolysis and large numbers of hypercontracted fibres, both apparently the direct result of prolonged rigidity, not of hyperthermia.

Brinkman and Puschel [4] examined five fatal cases of MH histologically. The age of the subjects varied between 4 and 22 yr, and the temperature reached during the episode always exceeded 42 °C. Abnormalities were found in the skeletal muscles of all five patients. Internal nuclei (diffusely spread in the illustration) and some atrophied fibres were interpreted as evidence of a pre-existent myopathy, whereas acute necrosis and hypercontracted fibres were by implication the consequence of the episode. Hypercontracted fibres were also found in the myocardium.

Hull, Muller and Albrecht [22] described a biopsy in a boy of 8 yr, made just over 2 months after an episode of MH in which rigidity and an increase in temperature of 3.4 °C occurred. Apart from internal nuclei, not very numerous, the abnormal findings were ultrastructural: there were a few myelin bodies and mitochondria were abnormally numerous, enlarged and misshapen; however, mitochondria are normally numerous before puberty and the other features have the ring of artefact.

Kozlowski [31] reported the case of a boy aged 13 yr who died in malignant hyperthermia. The usual hypercontracted fibres were found and convincingly illustrated.

Weitz and Hubner [44] described in a young man of 17 yr the amount of regeneration that occurred in the 45-day interval between an MH episode and death. Three biopsies were obtained from different sites during the period of survival. The first biopsy from rectus abdominis taken during the crisis showed fibre calibre variation and internal nuclei, but no muscle necrosis. A second biopsy on the 4th day on the gastrocnemius showed segmental necrosis, and a third biopsy on the psoas on the 22nd day after operation also showed single fibre necrosis with reaction. Supercontracted fibres were seen in all three biopsies and were regarded as artefact. By the time of the postmortem, large focal areas of old necrosis were found, with fibre calcification, phagocytosis, regeneration and granulation tissue.

Kimura and colleagues [28] reported on fatal MH in a 44-yr-old female. There was muscle rigidity and an increase in temperature to 42 °C within 1 h of the administration of suxamethonium. Red urine was observed even though extensive sampling of skeletal muscle failed to show necrosis. The kidneys showed tubular necrosis, ascribed to circulatory insufficiency. The authors found that myoglobin also leaked out of muscle in a postmortem control, but did so by one order of magnitude less than from the patient's tissue. This might mean that increased membrane permeability well short of necrosis (subnecrosis) could account for myoglobinuria in some patients.

Histopathology of muscle biopsies performed in the Leeds MH Investigation Unit 1971–1986

It has been a salutory experience to study and report on all 1400 of the motor point biopsies performed in the Unit. At the beginning all abnormalities that were seen in the MH susceptible were assumed to be a manifestation of MH myopathy. By the time a small number of biopsies had been read, there were some 20 different findings, including fibre size variation, fibre splitting, predominance of one or other main fibre type, cytoplasmic bodies, tubular aggregates, single fibre atrophy, necrosis/regeneration and spotted fibres. A more puzzling feature also appeared early in the study when it was noted that many of the MH susceptible biopsies turned out to be normal by all methods of study used, histochemical, electron microscopical and of the innervation. Over a long period many of the individual components of "MH myopathy" were found also in MH insusceptible muscle, in small or moderate numbers. This did not necessarily exclude individual abnormalities from being related to MH myopathy, but meant that their occurrence in normal muscle seriously reduced their diagnostic value. The reason for the presence, although very infrequent, of abnormalities in asymptomatic, normal muscle is obscure: in the vastus muscle invariably biopsied in this series, trauma long past, and various forms of fibre or fibril malformation can be suggested. They have not been seen in the past, but that is because of the scarcity of normal muscle for examination at biopsy. As the use of whole muscle sections at postmortem becomes more widespread, such aberrations are likely to be discovered more often.

In the end, no features totally specific for MH myopathy emerged—a common experience in most myopathies. However, there were three abnormalities not seen in the MH insusceptible biopsies but known to be present in some other myopathies distinguishable from MH myopathy. The myopathic changes characteristic and diagnostic of MH myopathy that emerged from this study were *diffusely distributed internal nuclei, moth-eaten fibres and cores* (terms such as targetoid and core-targetoid are no longer used). The term "diffuse" applied to internal nuclei is used advisedly, as focal collections of internal nuclei, especially in the neighbourhood of fibrous seams, are not abnormal, but related to fibre attachments. Internal nuclei to be considered abnormal should be present in most fascicles in the section in at least 3 % of fibres. The aetiology of internal nuclei in MH is not known, but it is pertinent to note that greater numbers of internal nuclei occur in myotonic dystrophy and rarely in myotonia congenita.

Moth-eaten fibres and cores may be considered together as they have features in common and are often seen together in the same section. Both are best seen, and moth-eaten fibres only seen, in histochemical stains for oxidative enzymes (NADH-TR, succinate dehydrogenase). Both stains display the closely packed mitochondria present in type 1 fibres in which moth-eaten changes and cores will be found. "Moth-eaten" means a type 1 fibre altered by one or more areas of pallor, of irregular outline and soft edge. The pallor is the result of the disappearance of all or most mitochondria from the pale foci. These are not spaces: unstained, intact myofibrils can be detected within them. Moth-eaten fibres are easily simulated by artefact and require careful evaluation.

Cores differ from moth-eaten fibres in possessing round, sharply defined areas of pallor with complete absence of mitochondria within. By optical microscopy, myofibrils are normal, but older cores will show degenerative changes in central myofibrils. Both features may be accompanied by fibre size variation.

The ultrastructure of moth-eaten fibres is quite simple: areas of loss or reduction of mitochondria and occasionally a few fibrils with limited Z-band streaming. Cores show clearly outlined loss of mitochondria and varying amounts of Z-band streaming up to fusion and disintegration. The histopathology of MH myopathy has been described and illustrated elsewhere [15–18]. The essential changes in MH myopathy suggest to the writer that the functional disturbance in MH causes Z-band streaming by severe contraction of individual myofibrils. The fact that the myopathy is seen only in a minority of MH susceptible biopsies suggests that the contraction occurs silently, possibly at times of stress, and only occasionally is severe enough to cause the structural defect.

The literature on Malignant Hyperthermia Myopathy, that is, on the histopathology that can be directly related to the MH trait, is disappointingly small, given the number of centres in the world making open biopsies for *in vitro* tests. Usually, fully equipped centres do not publish histopathology. Those without facilities for tests diagnose on the basis of careful history taking and CK concentrations, and biopsy those who are likely to be MH susceptible. When only small numbers of patients are described, the peculiar features of MH myopathy are not observed, such as its occurrence in a minority of MH susceptible subjects, and the small number of characteristic changes (internal nuclei, core and moth-eaten fibres), despite the large variety of abnormalities observed overall. These require to be controlled by MH insusceptible biopsies. It requires many biopsies to discover that the majority of susceptible patients have histologically normal muscle.

The proposal by some authors that the histopathology of MH indicates a neuropathy or at least a neuromyopathy is of concern, for the writer is aware that biopsies on the vastus medialis as practised in the Leeds series cannot eliminate completely the possibility of a distal neuropathy. It is true that Reske-Nielsen found definite collateral re-innervation, but nearly always in the palmaris longus, on which the effect of involution on the innervation is not known. Furthermore, collateral re-innervation without other signs of neurogenic diseases such as large group atrophy, indicates only a healed neurogenic process. Other authors used type grouping and group atrophy too small to be currently acceptable.

The reason why fully equipped centres fail to include histopathology in their investigation of MH susceptibility is not hard to understand. They feel it is unnecessary for diagnosis, and it is true that there are few occasions on which histopathology can help the *in vitro* tests. The benefits of histological investigation should not be forgotten, however: the definition of MH myopathy, of post-MH myopathy and rhabdomyolysis, the recognition of muscle reactions to systemic disease and the recognition of associated myopathies can be important to the patient.

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PREOPERATIVE ASSESSMENT OF RISK FACTORS

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Despite the fact that it has been claimed that malignant hyperpyrexia (MH) is the single largest cause of anaesthetic mortality in apparently fit young patients, there has not really been a comprehensive attempt to predict the disease before anaesthesia. Whilst screening procedures such as those involving muscle biopsy are reliable, methods for investigating members of the family of a known or suspected case of MH are invasive, and often stressful. The ultimate goal still remains a non-invasive or simple clinical test which could detect the MH susceptible patient before anaesthesia.

Since it was first described, MH has been linked with a wide range of physical abnormalities and symptoms, knowledge of which may aid the clinician in the identification of patients at risk. However, to date there has been no systematic attempt to utilize this knowledge to produce a non-invasive diagnostic index. Individual abnormalities such as whether a patient has a squint, have been used to try and aid prediction [14], but until recently no research has been conducted to examine the predictive power of a wide ranging combination of abnormalities.

The development of any predictive diagnostic index is reliant, not only on diligent clinical observations, but also on the utilization of a sophisticated statistical technique. One such statistical procedure, discriminant function analysis, is particularly useful in the prediction of group membership. Suppose that, for practical purposes, members of a population can be divided into distinct groups with respect to certain characteristics, such as symptoms. For example, it is common practice in psychiatry to classify patients into diagnostic categories. Given a sample of patients allocated to diagnostic groups, one might wish to validate the diagnosis by use of empirical research, on the basis that new variables, or symptoms, may be derived to enable new decision rules to be implemented for the allocation of new patients to diagnostic categories. Not only does this approach provide new insights to the various diagnostic categories, but it also enables the clinician to minimize misclassification, or wrong diagnosis. This is a typical situation in which discriminant function analysis can be useful.

One application, then, of discriminant function analysis, is the prediction of group membership on the basis of a combination of appropriate symptoms. If a univariate statistical technique, such as analysis of variance, is used in data analysis, we are generally only asking whether group membership produces a significant difference on any one pre-determined variable. For example, in a recent study by Simpson, Smith and Davies [8], patients were given either atropine or glycopyrrolate as part of the anaesthetic process, and a univariate analysis of variance was used to determine whether postoperative cognitive impairment was associated with group membership and, consequently, which drug had been administered. Whilst this particular statistical analysis was valid for research of this nature, it only tells us whether the two groups of patients are significantly different in terms of postoperative cognitive impairment. It does not mean that, if we knew the level of cognitive impairment in any individual patient, we could accurately deduce which drug they were administered. Consequently, in this example, statistical significance does not imply a reliable method of prediction, only that the discrimination between groups is better than chance.

In the context of MH then, given that our goal is the development of a diagnostic index, we need a method of data analysis that will provide reliable decision rules for the classification of new patients. Used correctly discriminant function analysis can help us achieve this goal. Tabachnick and Fidell [13] provide an excellent account of the use of

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discriminant function analysis, for those with a mathematical aptitude.

DISCRIMINANT FUNCTION ANALYSIS IN MALIGNANT HYPERPYREXIA

As shown in table I, MH has been linked with a wide range of physical abnormalities and medical illnesses. Smith and colleagues [10] devised a novel questionaire covering these items, and sent it to 279 patients who had undergone diagnostic muscle biopsy for suspected MH. A further 196 questionnaires were sent to a control group of patients who had undergone an equivalent operation/anaesthetic but who had had no reported anaesthetic reaction. The control group were matched for age and sex to those patients diagnosed MHS from the muscle biopsy group.

Ninety-six MHS patients, 79 MH negative patients and 168 control patients returned the questionnaire. Using the two diagnostic categories and control group as grouping indicators, all the variables on the questionnaire were subjected to discriminant function analysis, which proved capable of significantly discriminating the three patient groups (canonical correlation 0.64; $P < 0.0000$). Examination of the results indicated that an interaction of 20 variables from the questionnaire was responsible for this discrimination (table II).

Using these variables to classify patients into the three different patient groups, an overall agreement with diagnostic classification of 71% was obtained (table III).

TABLE I. *Abnormalities and medical illness observed in MH susceptible patients* [1–4]

Personal	Family History
Squint	Squint
Ptosis	Ptosis
Hernia	Hernia
Kyphoscoliosis	Kyphoscoliosis
Dislocated joints	Dislocated joints
Slipped disc	Slipped disc
Feet abnormalities	Feet abnormalities
Muscle, bone and joint disease	Muscle, bone and joint disease
Undescended testicle	Heart disease
Heart disease	Bleeding
Diabetes	Sudden death
Cramp	Congenital abnormalities
Muscle weakness	Cot deaths
Blackouts	
Temperature changes	
Anxiety	
Sports injuries	

TABLE II. *Summary of factors (increased incidence of variable) discriminating MH positive group of patients from other patient groups* [10]

Previous postoperative problems
  Fever
  Muscle swelling
  Muscle weakness

Personal history
  Squint
  Backache
  Heart disease
  Muscle cramps
  Muscle weakness
  Blackouts
  High fevers
  Febrile convulsions
  Anxiety
  Road accidents

Family history
  Squint
  Foot abnormality
  Muscle, bone and joint disease
  Diabetes
  Bleeding
  Cot deaths
  Congenital abnormality

In simple terms what Smith and colleagues found [10] was that a weighted interaction of 20 variables was capable of predicting MHS patients with a classification accuracy of 61.5%, when compared with the results of muscle biopsy. Potentially, what this means in practical terms is that, if we have information from any patient regarding the 20 important variables, we can diagnose MH susceptibility with an accuracy of 61.5%, compared with invasive muscle biopsy. Whilst this screening technique cannot yet reproduce the diagnostic accuracy of muscle biopsy, it provides a foundation for further research and development. It even offers the future potential of screening every patient before anaesthesia, once its classification accuracy is improved.

Several studies are currently in progress to improve the discriminative accuracy of the questionnaire. For example, one of the predictive variables highlighted by the questionnaire is that of anxiety. From a theoretical point of view, the emergence of this variable possibly provides support to the idea first postulated by Wingard [15] that MH is a type of familial stress syndrome. A further study by Smith, Newbegin and Ellis [9] provides yet more evidence that this hypothesis is

TABLE III. *Classification results* [10]

Actual group	No. of patients	Predicted group membership 1	2	3
Group 1 (Control)	168	136 81.0%	17 10.1%	15 8.9%
Group 2 (MHS)	96	18 18.8%	59 61.5%	19 19.8%
Group 3 (MH negative)	79	20 25.3%	12 15.2%	47 59.5%

plausible. Twenty-one consecutive, suspected MH probands were asked to complete the State–Trait Anxiety Inventory [12] before undergoing muscle biopsy. State anxiety was found to correlate significantly ($P < 0.01$) with the results of muscle biopsy, with MHS patients showing significantly higher levels of "pre-biopsy" anxiety than their MH negative counterparts.

High levels of anxiety are a frequent "symptom" of surgical procedures [7]. Physiologically, such anxiety is usually accompanied by changes in the hypothalamic–pituitary–adrenal (HPA) axis, and several papers report that the HPA axis altered during and following surgery, with plasma ACTH and cortisol concentrations increasing dramatically in the period immediately after operation [5, 6]. A recent pilot study by Smith and colleagues [11] indicated that certain indices of HPA axis activity are also capable of differentiating MHS patients from their MH negative counterparts.

MHS patients show significantly higher concentrations of glucose and growth hormone following muscle biopsy, compared with their MH negative counterparts. A discriminant function analysis comparing 20 MHS patients with 30 MH negative patients on a variety of HPA axis indices proved capable of significantly discriminating the two groups with an accuracy of 85% (canonical correlation 0.75, $P < 0.0000$).

Prospective studies are currently in progress utilizing all three lines of research, in an attempt to develop a non-invasive preoperative assessment of risk factors that could be used as a diagnostic screening battery.

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RATE OF INACTIVATION OF HUMAN AND RODENT HEPATIC METHIONINE SYNTHASE BY NITROUS OXIDE

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COMPARISON OF TOTAL VENTILATORY COMPLIANCE DURING ANAESTHESIA IN SPONTANEOUSLY BREATHING AND PARALYSED INFANTS AND YOUNG CHILDREN

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A reduction in compliance following induction of anaesthesia has been demonstrated in adults and it has been reported that the administration of a neuromuscular blocking drug has no significant further effect [1]. Although it is common to paralyse and ventilate infants and young children during anaesthesia, there is little documented evidence of the effects of anaesthesia, neuromuscular blockade or the pattern of ventilation on lung mechanics in this age group.

Total ventilatory compliance (C_{rs}) was measured in anaesthetized infants using the occlusion technique, which has been validated in this department [2].

In contrast to adults, preliminary results showed values of C_{rs} which were sometimes significantly higher during paralysis and controlled ventilation than during spontaneous ventilation.

To investigate whether this phenomenon was related to the pattern of ventilation during paralysis, a study was designed in which C_{rs} was measured before operation under anaesthesia (a) while the infant breathed spontaneously, (b) following administration of a neuromuscular blocking drug with the pattern of ventilation closely mimicking that during spontaneous breathing and (c) during paralysis, but with tidal volumes of at least double that observed during spontaneous breathing. Studies were performed on 15 subjects aged from 70 days to 25 months.

Most values of C_{rs} obtained during paralysis with small tidal volumes (B) were very similar to those recorded during spontaneous ventilation (A), whereas marked increases in C_{rs} (up to 100%) occurred during ventilation with greater tidal volumes (C) (fig. 1).

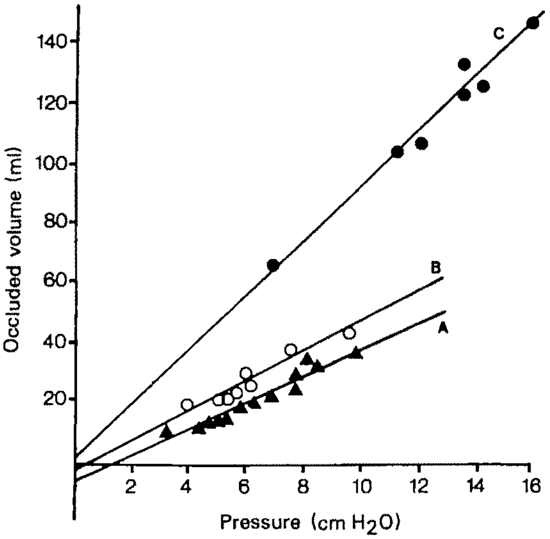

FIG. 1. Volume–pressure plots of an 8-kg infant. A: $C_{rs} = 4.5$; B: $C_{rs} = 5.2$; C: $C_{rs} = 9.4$ ml/cm H_2O.

These results suggest that, whereas paralysis *per se* has little effect on compliance, the tidal volume during ventilation may have a marked influence on lung mechanics. If meaningful conclusions are to be drawn regarding the effects of anaesthesia in infants, measurements both before and after induction should be obtained during spontaneous ventilation.

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EFFECT OF BETA-1 AND BETA-2 BLOCKADE ON ISOPRENALINE INDUCED HYPOKALAEMIA IN DOGS

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Isoprenaline causes hypokalaemia in animals and in man and some workers have reported a small increase in plasma

TABLE I. *Plasma potassium* (*mmol litre*$^{-1}$) (*mean* (*1SD*)) *during isoprenaline infusion in dogs.* * *Significant difference from pre-infusion value* (*P* < *0.001, analysis of variance and Wilcoxon's test for paired data*)

		Pre-inf. K^+	Maximum K^+	Minimum K^+
Control	($n = 10$)	3.65(0.35)	3.72(0.37)	2.86(0.22)*
Beta-1 blockade	($n = 10$)	3.42(0.47)	3.51(0.48)	2.90(0.53)*
Beta-2 blockade	($n = 10$)	3.12(0.22)	3.15(0.23)	2.65(0.09)*

potassium (K^+) concentration before the hypokalaemic phase [1]. Species variation is a feature and the initial increase in K^+ has not been a constant finding in dogs. A combined alpha- and beta-adrenergic effect leading to K^+ release from the liver causes the initial increase in K^+ [2], whereas the hypokalaemia is said to be secondary to specific beta-2 stimulation and consequent K^+ uptake at hepatic and skeletal muscle sites [3].

Six adult beagles were anaesthetized with thiopentone and pentobarbitone. Ventilation was controlled, but no neuromuscular blocking drugs were used. pH was maintained in the range 7.35–7.44 and $Pa_{O_2} > 14.0$ kPa. The animals were allocated to one of three groups to receive: no beta blockade (control); atenolol 0.5 mg kg^{-1} (beta-1 blockade); ICI 118551 0.5 mg kg^{-1} (beta-2 blockade). Isoprenaline 0.1 μg kg^{-1} min^{-1} was infused for five 30-min periods in each dog and a 30-min period of 0.9% saline infusion preceded and followed each drug infusion. Arterial K^+ was continuously monitored using a valinomycin based K^+-sensitive electrode placed in the abdominal aorta via a femoral artery.

Table I shows the results. A transient increase in plasma K^+ was seen within 5 min of starting each drug infusion in the control and beta-1 groups, whereas only seven of 10 infusions caused such an increase in the beta-2 group. The increases were small and probably of no clinical significance. There followed a more profound decrease in plasma K^+ during all 30 infusions of isoprenaline and this hypokalaemia was sustained for the duration of the infusion. The maximum decrease in K^+ concentration noted was 1.09 mmol litre^{-1} during an infusion in the control group.

The isoprenaline-induced decreases in K^+ concentration were 0.79(0.17), 0.52(0.19) and 0.47(0.18) mmol litre^{-1} in the control, beta-1 and beta-2 blocked animals, respectively. The decrease was greatest in the control group ($P < 0.005$, analysis of variance and Wilcoxon's test for non-paired data), but similar in the beta-1 and beta-2 groups.

The biphasic nature of the K^+ response to isoprenaline infusion in dogs has been confirmed in this study. In addition, pretreatment was either beta-1 or beta-2 blockade was seen to attenuate isoprenaline-induced hypokalaemia.

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TRANSCONJUNCTIVAL AND TRANSCUTANEOUS OXYGEN MONITORING: *IN VIVO* STABILITY

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The transconjunctival oxygen sensor consists of a miniature Clark type electrode and a thermistor imbedded in a polymethylmethacrylate ocular conformer which records the oxygen tension at the inner surface of the upper eyelid (Pcj_{O_2}). Because the distance between electrode and capillaries is so small, no heating element is required. Pcj_{O_2} is said to reflect changes in both cardiac output and arterial oxygen tension, but before it can be used as a non-invasive trend monitor of oxygenation, stability *in vivo* under stable clinical conditions should be documented. The *in vivo* and *in vitro* stability of a transconjunctival oxygen sensor (Biomedical Sensors Ltd), a combined oxygen and carbon dioxide electrode (Novametrix 850, Vickers Medical Ltd) and a pulse oximeter (Biox IV, Ohmeda Ltd) were therefore evaluated in 10 normal adults.

The conjunctival and transcutaneous electrodes were re-membraned and had two-point gas calibrations before use. The former was positioned in the conjunctival sac after instillation of local anaesthetic (0.4% w/v oxybuprocaine); the latter was operated at 45 °C and attached to the left arm using double-sided adhesive rings. The oximeter probe was placed on the left middle finger, and the monitor operated in the fast mode. The outputs from each monitor were displayed continuously on a chart recorder. Steady state Pcj_{O_2}, transcutaneous oxygen (Ptc_{O_2}) and carbon dioxide (Ptc_{CO_2}) and oxygen saturation (Sa_{O_2}) were averaged over 4 min 30 min after application of the sensors (baseline) and then at the end of the study 3 h later. Drift was defined as a change in the final readings (+/−) from baseline values. Values recorded by the sensors for a gas calibration standard (5% carbon dioxide + 12% oxygen + 83% nitrogen, Corning Medical Ltd) before and after the *in vivo* study permitted *in vitro* drift to be calculated.

TABLE II. *Mean* (*SD*) *steady state* in vivo (*A*) *and* in vitro (*B*) *values.* *P < *0.05*

		Sa_{O_2} (%)	Pcj_{O_2} (kPa)	Ptc_{O_2}	Ptc_{CO_2}
(A)	Start	97 (1 3)	8.0 (1.3)	12.7 (1.7)	6.0 (0.3)
	End	97 (1.1)	8.5 (1.3)	15.6 (2.5)*	5.9 (0.3)
(B)	Start	–	12.4 (0.6)	12.7 (1.4)	3.5 (0.1)
	End	–	12.3 (0.6)	15.2 (1.9)*	3.5 (0.2)

No significant change in Sa_{O_2}, Pcj_{O_2} or Ptc_{CO_2} occurred despite a 23% increase in Ptc_{O_2} (table II). *In vitro* drift partly accounted for the increase in Ptc_{O_2}, but could not be relied on to predict the size of the *in vivo* drift. It explained only 13% of the variance.

None of the above sensors can accurately predict arterial oxygen tension (Pa_{O_2}). This had led to the concept of a ratio between Pcj_{O_2} or Ptc_{O_2} and Pa_{O_2}. The present data suggest that, under steady state conditions, such a ratio remains constant for Pcj_{O_2}, but not for Ptc_{O_2}.

PERIOPERATIVE HAEMODYNAMIC CHANGES DURING AORTIC VASCULAR SURGERY: COMPARISON BETWEEN OCCLUSIVE AND ANEURYSMAL DISEASE STATES

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Myocardial infarction accounts for 50% or more of the postoperative mortality associated with abdominal aortic surgery. Aortic cross-clamping and unclamping is accompanied by changes in cardiac index (CI) and systemic vascular resistance (SVR) which may be poorly tolerated in patients with coronary artery disease [1]. Previous studies evaluating the haemodynamic responses to aortic clamping and unclamping have combined data from patients undergoing abdominal aortic aneurysm (AAA) resection and aortobifemoral bypass (ABB) grafting [2]. The aim of this study was to compare the haemodynamic changes that occur during aortic clamping and unclamping in patients undergoing AAA and ABB procedures.

Following ethics committee approval and informed consent, 30 ASA II–III patients scheduled for elective aortic vascular surgery underwent preoperative determination of left ventricular ejection fraction (LVEF) using radionucleotide scanning. Group I ($n = 18$) underwent AAA repair, group II ($n = 11$) underwent ABB grafting. A standardized anaesthetic technique was used for all patients studied. Radial and pulmonary artery catheters were inserted under local anaesthesia. Induction of anaesthesia and muscle paralysis were facilitated using i.v. thiopentone 2–3 mg kg^{-1}, fentanyl 4 µg kg^{-1} and pancuronium 0.1 mg kg^{-1}. Controlled normocapnic ventilation was then commenced with 66% nitrous oxide in oxygen and 0.5–1% isoflurane. Pulmonary occlusion pressure was maintained between 10 and 15 mm Hg and hypertension > 20% of baseline was controlled by infusion of nitroglycerin. Measured and derived haemodynamic data were obtained before and after induction, aortic cross-clamping and unclamping. Statistical analysis included Duncan multiple range testing and repeated measures of analysis of variance.

The aorto-occlusive patients were younger, required less perioperative fluids and had a longer aortic clamp time. Cross clamping of the aorta was associated with significant increases in SVR and mean arterial pressure (MAP) and decreases in CI in both groups. Changes in CI, SVR and left ventricular stroke work index (LVSWI) during aortic cross-clamp and unclamp differed significantly between the two surgical procedures (fig. 2).

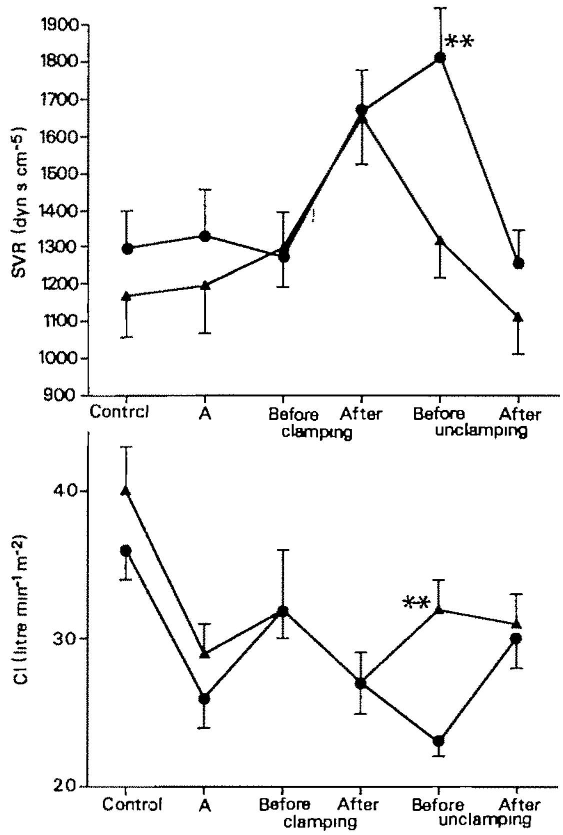

FIG. 2. Changes in cardiac index (CI) and systemic vascular resistance (SVR) (mean ± SEM) in patients undergoing occlusive (▲) or aneurysm (●) surgery. **$P < 0.01$. A = Anaesthesia.

In this study patients undergoing ABB grafting demonstrated a more stable haemodynamic profile during aortic-clamping and unclamping than those having AAA resection. Chronic collateral circulation associated with aorto-occlusive disease may permit continuous lower extremity perfusion during aortic clamping.

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USE OF DIFFERENT DOSES OF NEOSTIGMINE TO ANTAGONIZE NEUROMUSCULAR BLOCKADE BY ATRACURIUM

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The antagonism of neuromuscular block produced by atracurium 0.5 mg kg^{-1} is as rapid with neostigmine 2.5 mg as with neostigmine 5.0 mg, if antagonism is attempted when the ratio of the first compound action potential of the train-of-four (A′) is 10% of control (A) [1]. The efficacy of neostigmine 1.25 mg and 0.625 mg neostigmine in antagonizing the same degree of block has been studied using an identical procedure.

Anaesthesia was induced with droperidol, fentanyl and thiopentone and maintained with nitrous oxide whilst control values of the electromyographic response (EMG) of the adductor pollicis muscle to trains of four supramaximal stimuli applied to the ulnar nerve were recorded. Atracurium 0.5 mg kg^{-1} was then given and EMG monitoring was continued. Increments of fentanyl and atracurium were given as required, but no volatile agent was used. EMG recordings were analysed using the ratio of the first response to control (A′/A) and the ratio of the fourth to the first (D′/A′). At the end of surgery, and when the height of A′/A had returned to 10%, neostigmine 1.25 mg or 0.625 mg was given (with atropine) depending on a random allocation of patients. EMG monitoring continued until D′/A′ had attained 70% for at least 20 min.

All the results, including those of Fox, Keens and Utting [1], are summarized in table III.

TABLE III. *Times (mean, SD) to 70% recovery*

Dose (mg)	No.	A′/A (min)	D′/A′ (min)
None [1]	10	25.0 (9.5)	32.3 (10.4)
0.625	11	13.0 (4.3)	19.3 (5.6)
1.25	13	9.89 (4.7)	14.2 (6.9)
2.5 [1]	10	8.2 (2.9)	12.0 (3.5)
5.0 [1]	5	7.4 (1.7)	11.2 (2.3)

All four doses of neostigmine accelerated recovery (unpaired *t* test: $P < 0.01$ for both variables). There was no statistical difference in the rates of recovery for the three larger doses, but the smallest dose (0.625 mg) produced a slower rate than the two higher doses. Neostigmine 2.5 mg is adequate to antagonize blockade at least when some degree of recovery is apparent, but although a dose of 1.25 mg may be sufficient, 2.5 mg is probably more convenient and reliable; neostigmine 0.625 mg is insufficient.

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ATRACURIUM AND VECURONIUM FOLLOWING TUBOCURARINE

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An incremental dose of myoneural blocker is often used to prolong an existing neuromuscular blockade. The use of one of the newer short acting agents to prolong an established blockade from a longer acting agent should offer the advantages of both economy and ease of antagonism [1]. We therefore studied the effect of atracurium or vecuronium after tubocurarine.

Following ethical committee approval, 30 ASA I or II patients undergoing major gynaecological procedures were studied. All received premedication with oral lorazepam. Anaesthesia was induced using thiopentone, fentanyl and droperidol, and ventilation assisted with 67% nitrous oxide in oxygen to maintain normocapnia. Neuromuscular transmission was monitored using trains of four supramaximal stimuli applied to the ulnar nerve every 20 s with recording of the integrated evoked compound EMG from the adductor pollicis muscle (Datex Relaxograph). A neuromuscular blockade to approximately 90% inhibition of the first response of the train (T1) was established using tubocurarine. The trachea was intubated, and ventilation continued to normocapnia. When the T1 response had recovered to 10% of control, an increment of either atracurium or vecuronium was given i.v. The same dose of the same drug was repeated at each subsequent return of T1 to 10%. The patients were divided into three groups: group 1 received atracurium 1.1 mg, group 2 atracurium 2 mg, and group 3 vecuronium 0.25 mg (atracurium 1.1 mg and vecuronium 0.25 mg are equipotent [2]). The mean ages and weights of the patients in the three groups were similar.

In all the cases the duration of action of the first increment was the longest: group 1 (atracurium 1.1 mg) 8.0 min, group 2 (atracurium 2 mg) 13.8 min, and group 3 (vecuronium) 17.1 min. This decreased with successive increments until the duration of each was constant. This occurred after the fourth increment with group 1 (range 5.8–6.9 min), the fourth increment with group 2 (range 9.1–9.9 min), but not until after the 7th increment with group 3 (range 5.6–5.8 min).

The duration of action of either vecuronium or atracurium is extended in the presence of tubocurarine, an effect which decreases with time as the action of tubocurarine wanes. A tubocurarine neuromuscular block can be reliably prolonged with a small dose of either atracurium or vecuronium.

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APROTININ REDUCES THE NECESSITY FOR DONOR BLOOD TRANSFUSIONS IN PATIENTS HAVING CARDIAC SURGERY

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SUPPLEMENTARY ISOFLURANE ON CARDIOPULMONARY BYPASS

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In recent years the mainstay of anaesthesia for cardiac surgery has been the use of high or moderate dose opiate techniques, with or without a volatile supplement. The increase in cardiac surgical workload and the increasing scarcity of intensive care nurses has encouraged us to seek techniques that will permit earlier extubation of the trachea [1] and consequently shorten the patient's stay in the intensive care unit. Such techniques have included continuous opiate infusions [2], which avoid the requirement for cumulative boluses, and the reduction of the size of bolus used. Recently a volatile anaesthetic agent, usually isoflurane, has been added via the fresh gas flow to the oxygenator during cardiopulmonary bypass (CPB) [3] to improve the level of anaesthesia and to reduce or eliminate the need for i.v. opioid or sedative supplements. This study explored the use of isoflurane on CPB and its effect on requirements for anaesthetic and haemodynamic intervention, extubation, recall and postoperative analgesia.

Fifty patients scheduled for elective first operation for coronary artery disease were randomly allocated to two equal groups. All patients were younger than 70 years and were free from major neurological, psychiatric and personality disorders. During CPB group A received 1% isoflurane in the fresh gas flow to the oxygenator, and group B received no inhalation supplement. A procedure for the administration of supplementary i.v. anaesthetic agents was established and adhered to in both groups. A record of all anaesthetic agents, vasoconstrictors and vasodilators administered was kept for each patient. Statistical analyses were performed with the unpaired *t* test, the Mann-Whitney *U* test and the Chi-squared test.

Significant differences were found between the two groups for all drugs administered. Significantly less metaraminol ($P = 0.008$) and more phentolamine ($P = 0.046$), fentanyl ($P = 0.023$) and pancuronium ($P = 0.019$) were administered in group B. There was no significant difference in time to tracheal extubation, but there was significantly more recall of intensive care and perception of vivid postoperative dreaming in group B.

Isoflurane administred during cardiopulmonary bypass reduces the requirement for i.v. anaesthetic supplements and vasodilators. The diminished recall of intensive care and the lessened perception of postoperative dreaming may enhance the subjective quality of recovery.

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EFFECTS OF ATRACURIUM AFTER PANCURONIUM

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Atracurium may be used for long surgical procedures by infusion or by intermittent injections. Such methods offer the advantage of fast recovery of muscle action, but may not be economical. The use of pancuronium followed by atracurium may offer advantages of economy and rapid recovery. A previous study using vecuronium after pancuronium showed that the interaction between these drugs initially extends the duration of effect of vecuronium [1].

The aim of this study was to investigate the duration of effect of atracurium administered after pancuronium.

Eleven patients requiring prolonged major surgery were given pancuronium 0.055 mg kg^{-1} i.v. following induction of anaesthesia using thiopentone and fentanyl. The trachea was intubated and the patient was ventilated to normocapnia using 70% nitrous oxide in oxygen. Neuromuscular transmission was monitored using train-of-four supramaximal stimuli to the ulnar nerve every 20 s, the integrated evoked compound action potential at the adductor pollicis being recorded.

At a clinically appropriate level of recovery of neuromuscular transmission, where the response to the first stimulus (T1) was 10–20% of the control response, a dose of atracurium 1.1 mg was given i.v. The same dose was repeated the next and every subsequent time that the same level of response was achieved until recovery was allowed towards the end of surgery

Eleven patients were studied: nine received six doses of atracurium and the other two patients received five doses. The mean durations of effect of each dose were 11.9 min for the first dose then 9.14 min, 8.82 min, 7.86 min and 8.00 min for subsequent doses.

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PREOPERATIVE FLUIDS AND RANITIDINE IN CHILDREN

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Ranitidine is an H_2-receptor antagonist which has been shown to produce a significant reduction in preoperative gastric volume and acidity [1]. As yet there has been little reported on the use of ranitidine in children. Studies on preoperative fluid administration have produced contrasting results with some groups showing an increase in gastric volume in patients given fluids by mouth 2–3 h before surgery [2] and others showing no change or a reduction in gastric volume [3]. In this study we aimed to reduce preoperative starvation in children and to provide a safer gastric environment in the induction period.

The study was approved by the hospital ethics committee and parents gave written, informed consent. Eighty-eight children aged 1–14 yr, ASA I or II, who were admitted for minor surgery through Day Care were studied. They were allocated randomly to four groups for premedication as follows: group A = juice 5 ml kg^{-1} + placebo ($n = 23$); group B = juice 5 ml kg^{-1} + ranitidine 2 mg kg^{-1} ($n = 22$); group C = placebo ($n = 22$); group D = ranitidine 2 mg kg^{-1} ($n = 21$). All the study agents were administered 2–3 h before the scheduled time of surgery. Following induction of general anaesthesia, the gastric contents were aspirated using a 14-gauge orogastric tube. The position of the tube was confirmed by auscultation over the epigastrium, and the stomach emptied as completely as possible using a 60-ml syringe. The volume aspirated was recorded and the pH measured immediately.

Analysis of variance and unpaired *t* tests were used for statistical evaluation of the results and a *P* value less than 0.05 was considered significant. Patients in whom the period between premedication and aspiration was less than 1.5 h were excluded from statistical analysis.

There were no significant differences between the groups with respect to age, weight and period of fasting before premedication. The mean gastric volumes aspirated in each group were as follows: group A, 0.34 (SD 0.29) ml kg^{-1}; group B, 0.17 (SD 0.19) ml kg^{-1}; group C, 0.24 (SD 0.27) ml kg^{-1}; group D, 0.17 (SD 0.15) ml kg^{-1}. These results indicate a significant reduction in gastric volume in group B by the use of ranitidine, when compared with group A ($P < 0.05$)

The mean pH of the gastric aspirates were: group A, 1.84 (range 0.99–4.4); group B, 4.48 (2.0–7.7); group C, 2.01 (1.9–4.1); group D 3.8 (1.5–7.4). There was a significant difference between groups A and B ($P < 0.001$), and between groups C and D ($P < 0.01$).

The findings of this study indicate a significant reduction in gastric volume and acidity by the use of oral ranitidine premedication, even in children who have received oral fluids up to 1.5 h before operation.

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EFFECT OF ACUTELY ADMINISTERED PHENYTOIN ON NON-DEPOLARIZING NEUROMUSCULAR BLOCKADE

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Phenytoin produces a dose-related neuromuscular blockade in animals [1]. However, chronic phenytoin therapy in man results in resistance to non-depolarizing neuromuscular blocking agents [2]. The present study was designed to determine whether the acute administration of phenytoin, in a clinically relevant dose, would affect a non-depolarizing neuromuscular blockade.

The study was approved by the local ethics committee and informed consent obtained from each patient. Eight patients, aged between 30 and 62 yr and scheduled to undergo neurosurgical procedures which required perioperative anticonvulsant prophylaxis, were investigated. Patients with neuromuscular and cardiac disorders or receiving medication known to affect neuromuscular blockade were excluded.

Anaesthesia was induced with sodium thiopentone 3–5 mg kg^{-1}, fentanyl 3–4 μg kg^{-1}, and vecuronium 0.1 mg kg^{-1}. The trachea was intubated and anaesthesia maintained with 66 % nitrous oxide and 0.5–1 % isoflurane in oxygen. End-tidal carbon dioxide tension was maintained at 3.3–4.3 kPa and the nasopharyngeal temperature kept greater than 36 °C. Neuromuscular blockade was measured using stimulation of the ulnar nerve at the wrist with recording of the evoked compound EMG from the adductor pollicis muscle (Datex Relaxograph). Neuromuscular blockade was maintained at a constant level using an infusion of vecuronium adjusted to achieve a steady state blockade of the first twitch of the train-of-four (T1) between 5 and 10 % of that before neuromuscular blockade. After steady state neuromuscular blockade had been maintained for a minimum of 30 min an infusion of phenytoin 10 mg kg^{-1} was administered at a rate of 50 mg min^{-1}. The vecuronium infusion rate and the concentration of isoflurane were kept constant during this time. The T1 height before administration of the phenytoin was then compared with the T1 height at 15, 30, and 45 min after the beginning of the phenytoin infusion.

TABLE IV. *T1 % following administration of phenytoin (mean (SD))*

0 min	15 min	30 min	45 min
4.375 (1.41)	3.25 (1.9) $P < 0.02$	2.5 (1.5) $P < 0.001$	2.25 (1.71) $P < 0.01$

The T1 height was reduced following the administration of phenytoin at all three times (table IV) These changes were significantly different from the control values (paired *t* test) The absolute changes were small, and would be unlikely to be clinically significant.

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EFFECT OF SODIUM CITRATE *V.* RANITIDINE PRETREATMENT ON GASTRIC PEPSIN ACTIVITY IN NON-OBSTETRIC PATIENTS

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Gastric juice, free of food particles and at pH values well above 2.5, can cause hypoxaemia [1]. Gastric pepsin is a proteolytic enzyme active at pH 1–5 which may play a role in the causation of aspiration pneumonitis. In this study we have measured the pepsin activity in the gastric juice of patients fasted for elective surgery and investigated the effects of agents conventionally used to reduce acid aspiration risk factors [2].

One hundred and fifteen adults receiving general anaesthesia for elective minor gynaecological surgery were randomly assigned to one of three pretreatment regimens after informed consent (all patients were ASA I and received no other premedication): group 1 = no pretreatment ($n = 39$), group 2 = ranitidine 150 mg by mouth with 30 ml of water 2 h before anticipated time of surgery ($n = 37$); group 3 = 30 ml of sodium citrate 0.3 mol litre^{-1} immediately before transfer to theatre ($n = 39$).

Seven patients in whom no gastric sample was obtained were excluded from statistical analysis. All these had received pretreatment with ranitidine.

TABLE V. *pH, volume, pepsin activity and total pepsin (mean ± SEM) of gastric contents of patients in the three groups. By Mann–Whitney* U *test*: $P < 0.05$ v. **group 1 or †group 2*; $P < 0.001$ v. ***group 1 or ††group 2*

	n	pH	Volume (ml)	Pepsin activity (mg ml^{-1})	Total pepsin (mg)
Group 1	39	1.8	29.9 ± 3	1.08 ± 0.09	30.7 ± 3.6‡
Group 2	30	5.5**	16.4 ± 2.5**	0.79 ± 0.16*	13.0 ± 3.1
Group 3	39	4.6**†	42.8 ± 2.8**††	0.62 ± 0.12*	25.0 ± 2.8‡

An 18 French gauge Salem orogastric tube was introduced after induction of anaesthesia with thiopentone and alfentanil and all available gastric contents aspirated. Gastric samples were analysed for volume (standard burette); pH (calibrated pH meter); pepsin activity (Berstad's [3] method). All samples were immediately stored at 4 °C and analysed within 36 h.

The three groups were comparable for mean age, weight and fasting interval. The pretreatment to sampling interval for group 2 was 142 ± 8 min and for group 3 was 46.9 ± 3.1 min (mean ± SEM).

Results are summarized in table V. Ranitidine was as effective as sodium citrate in increasing the pH to greater than 2.5. The ranitidine group had the least residual gastric volume (16.4 ± 2.5 ml); sodium citrate group had the highest volume (42.8 ± 2.8 ml). These differences in volume between the three group were highly significant ($P < 0.001$). Both group 2 and group 3 patients had equally reduced pepsin activity compared with group 1, but when total pepsin (product of pepsin activity/ml and residual gastric volume) was considered, group 2 had significantly less total pepsin than the other two groups. Group 3 was similar to group 1, despite the higher residual volume.

We suggest that the protective effect of antacid therapy may be partly mediated by decreasing pepsin activity and that a single oral dose of ranitidine will reduce the total pepsin more effectively than will sodium citrate.

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ACCELERATING NEUROMUSCULAR BLOCKADE

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The rate of onset of a non-depolarizing neuromuscular blocking drug is increased by the prior administration of a small dose of the same drug [1]. This study investigates the effect of a small ("priming") dose of one blocker on the rate of onset of another.

Ethics committee approval was obtained for the study. Two myoneural blockers known to be strongly synergistic were chosen—tubocurarine and alcuronium [2]. The intubating dose of tubocurarine was 0.5 mg kg^{-1} and that of alcuronium 0.25 mg kg^{-1}. Priming doses were 10% of these. Informed consent was obtained from 48 patients (ASA I or II); these were divided into six groups (table VI). Lorazepam was given for premedication. Surface electrodes were placed on the wrist and hand for stimulating the ulnar nerve and recording the evoked compound EMG from the adductor pollicis muscle. A Medelec MS6 system was used, set to deliver trains of four supramaximal stimuli every 12 s. Anaesthesia was induced with thiopentone 5 mg kg^{-1} and fentanyl 2 µg kg^{-1} and ventilation assisted using 66% nitrous oxide in oxygen to maintain normocapnia. Stimulation and recording was begun and the priming dose given. After 3 min, during which time anaesthesia was maintained with further increments of thiopentone as required, the intubating dose was given. When maximum neuromuscular blockade was reached, the trachea was intubated and anaesthesia allowed to continue without constraint. The EMG amplitude of the first contraction of each train-of-four was measured and compared with that before administration of any neuromuscular blocker.

There was no significant difference between mean ages, weights or sex ratios across the groups. There was no measurable depression of neuromuscular transmission seen to result from the priming dose. The administration of a dose of the same blocker accelerated the rate of onset of the intubating dose. When a priming dose of the other blocker was given, the rate of onset of the main dose was further accelerated (table VI).

The rate of onset of an intubating dose of tubocurarine or alcuronium can therefore be markedly accelerated by the prior administration of a small dose of the other agent.

TABLE VI. *Percent blockade (mean ± SEM) achieved at various times after administration of neuromuscular blocking drugs (tubocurarine, alcuronium)*

1st Dose	2nd Dose	Time (s) 24	48	72
—	Tubo.	7.1 ± 4.6	40.8 ± 9.3	63.0 ± 8.2
Tubo.	Tubo.	9.9 ± 5.9	59.1 ± 6.1	78.3 ± 4.9
Alc.	Tubo.	20.0 ± 7.6	63.9 ± 8.2	83.1 ± 5.0
—	Alc.	8.2 ± 5.5	33.4 ± 8.8	56.3 ± 7.6
Alc.	Alc.	7.1 ± 5.6	46.3 ± 9.9	65.1 ± 10.7
Tubo.	Alc.	28.6 ± 7.6	69.3 ± 8.3	83.7 ± 4.4

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EFFECT OF WATER INGESTION AND DIAZEPAM PREMEDICATION ON GASTRIC VOLUME AND pH

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A previous study [1] suggested that diazepam by mouth reduces gastric acid secretion and does so more effectively than i.m. diazepam when given 2–6 h before operation. Patients in the oral premedication group were also given water 50 ml, the effect of which on gastric acidity and volume was not assessed.

In the present study, the effect of water ingested before operation and oral diazepam premedication on residual gastric volume and pH was examined using 60 healthy patients in groups of 15 scheduled to undergo elective surgery. Before operation, patients in group 1 were totally fasted, group 2 ingested 150 ml of water, group 3 ingested water 50 ml and diazepam 10 mg by mouth and group 4 received water 150 ml and diazepam 10 mg by mouth. Immediately after the induction of anaesthesia the stomach was emptied as completely as possible using a Salem sump tube and the volume and pH of residual gastric contents measured.

The results (table VII) show that there was no significant difference between any of the four groups in terms of residual volume or pH. In each group, 46–60% of patients could be considered at risk of pneumonitis in the event of aspiration, having gastric volumes greater than 25 ml with pH values less than 2.5 [2].

TABLE VII. *Mean (range) gastric volumes and pH values*

Group	Volume (ml)	pH
1	34.8 (14–95)	2.0 (1.3–7.1)
2	35.5 (3–112)	2.5 (1.3–7.3)
3	31.8 (5–78)	1.9 (1.4–4.9)
4	31.8 (3–85)	2.5 (1.5–7.1)

It would seem unnecessary for patients to abstain from drinking small quantities of water before operation if the last dose is at least 1 h before induction of anaesthesia. Oral diazepam does not appear to have any effect on gastric acidity or volume 1 h after its administration.

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TOWARDS PRACTICAL AUTOMATIC CONTROL OF NEUROMUSCULAR BLOCKADE WITH ATRACURIUM

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Automatic control of neuromuscular blockade using pancuronium has already been demonstrated [1], but its use prolonged the anaesthetic preparation period. Our objective was to develop a robust control system which could be used without unduly interrupting the smooth running of a normal theatre list. The system should hold blockade steady at 20% of baseline T1 (determined before administration of the neuromuscular blocker).

A proportional–integral (PI) system, incorporating a preloaded integral, was developed. Proportional and integral gains were derived from step tests using the Ziegler–Nichols method [2]. The value of the preloaded integral was determined empirically.

The study, which was approved by the hospital Ethical Committee, was carried out in 20 ASA I and II patients undergoing elective surgery. Patients were premedicated with temazepam 20–30 mg. Anaesthesia was induced with fentanyl 50–100 μg and thiopentone 3–4 mg kg^{-1} as appropriate. Baseline T1 readings were obtained with a Datex Relaxograph. Tracheal intubation was accomplished after the administration of atracurium 0.25 mg kg^{-1} when the T1 had decreased to 25% of baseline. Anaesthesia was maintained with 67% nitrous oxide in oxygen supplemented by 1% enflurane and fentanyl as indicated.

The Relaxograph measured the EMG at 20-s intervals and transferred data to an RML 380Z-D microcomputer. The computer instructed a Vickers IP3 syringe pump to give a flow of atracurium 500 μg ml^{-1} which was calculated using the PI algorithm and updated every 20 s. The quality of control after stabilization was assessed by calculating a root mean square deviation of points around the target (RMSD). Table VIII summarizes the steady state results.

TABLE VIII. *Steady-state results. RMSD = Root mean square deviation*

	Range	Mean	SD
Age (yr)	39–78	63	10
Weight (kg)	40–99	64	16
Mean T1 (%)	16.8–21.7	18.9	1.4
Duration (min)	21–77	40.7	16
Dose (μg kg^{-1} min^{-1})	4.2–8.6	5.5	1.2
RMSD (%)	0 3–1 5	0.9	0.4

We conclude that the method provides a degree of paralysis which, after an initial period of stabilization, adhered very closely to the target T1. Blockade was steady enough to allow studies of the possible effect on T1 of other drugs and physiological perturbations such as haemodilution or hypothermia.

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CARDIOVASCULAR CHANGES DURING FIBREOPTIC INTUBATION

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Mechanical stimulation of the anterior pharynx by the Macintosh laryngoscope blade may be an important component in the generation of the pressor response to tracheal intubation [1]. However, the flexible fibreoptic laryngoscope facilitates intubation without the need for direct pressure on this area. The object of this study was to compare the cardiovascular responses to fibreoptic intubation (FOI) with those of orthodox intubation.

Following local ethics committee approval, 43 ASA I and II patients aged 18–67 yr undergoing routine general surgery were studied. They were premedicated with lorazepam; anaesthesia was induced with thiopentone and alcuronium. The lungs were ventilated by means of a pharyngeal airway, face mask and Bain system for 5 min with 33% oxygen, nitrous oxide and 0.5% halothane. Ventilation was adjusted to maintain an end-tidal carbon dioxide concentration of 5–5.5%. Immediately before orotracheal intubation, patients were randomly allocated to either the control group, who were intubated with a Macintosh laryngoscope, or the fibreoptic group. The method of FOI used has been described by Witton [2] and required protraction of the tongue by an assistant After manipulation of an American Optical LS-6A fibreoptic laryngoscope into the trachea, it was used as a guide over which the tracheal tube was advanced. The arterial pressure and heart rate were recorded at 1-min intervals with a Dinamap 1846 automatic arterial pressure monitor and printer, and the time taken for each intubation was noted. Data were analysed using upaired Student's *t* test.

The trachea of two patients in the fibreoptic group could not be intubated within 1 min and these subjects were excluded from the trial. The mean time (SEM) required for fibreoptic intubations, 26.9 (1.9) s, (range 17–45) was significantly longer than that required for control intubations, 9.6 (0.8) (range 5–17) Intubation was associated with significant increases in heart rate and arterial pressures in both groups compared with pre-induction values. The heart rate was significantly higher in the fibreoptic group during the second 1 min after intubation. The maximal recorded increases in systolic and diastolic pressures when compared with pre-intubation values were significantly greater in the fibreoptic group. The post-intubation rate–pressure product was significantly higher in the fibreoptic group.

This technique of FOI seems to produce a more severe sympathetic response than orthodox intubation and may be contraindicated in patients in whom it is important to avoid hypertension and tachycardia.

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ACUTE PHASE PROTEINS AFTER CHOLECYSTECTOMY

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We have studied the acute phase protein response to cholecystectomy with three different forms of anaesthesia. We followed the approach of Simpson, Radford and Lockyer [1], but intended that our three forms of anaesthesia should have more markedly different effects on the stress response to surgery, or on cortisol concentrations.

Twenty-four ASA I patients underwent elective cholecystectomy having been allocated randomly to three anaesthetic groups of eight—a control group, an extradural group, and an etomidate group. Each group was named for the component of anaesthesia under test. The remaining features of anaesthesia were common to all groups: premedication with temazepam 20 mg; neuromuscular blockade with atracurium; maintenance with oxygen and nitrous oxide, with the effects of the "test" component, and with further small doses of halothane and fentanyl as needed; postoperative analgesia with pethidine 50–75 mg i.m. as required, at minimum intervals of 2 h.

The control group received a sleep dose of thiopentone followed by fentanyl 3 $\mu g\ kg^{-1}$ to represent fairly conventional anaesthesia. The extradural group received thiopentone, and, in an attempt to suppress the stress response, were given thoracic extradural blockade with 0.5% bupivacaine 5–10 ml and diamorphine 3 mg during operation and a postoperative extradural infusion of diamorphine 20 mg in saline 10 ml over 48 h. The etomidate group received etomidate 0.3 mg kg^{-1} for induction followed by an i.v. infusion of 0.5 mg min^{-1} until peritoneal closure—to suppress adrenal production of steroids

The postoperative requirement of pethidine was less in the extradural group than in the other two groups, and was consistent with a satisfactory extradural effect [2]. Nonetheless, the distribution of the time courses of cortisol concentrations were similar in the control and extradural groups. The cortisol concentrations were depressed in the etomidate group until the first morning after operation. The time courses of all of the acute phase proteins were similarly distributed in all three groups.

We suspect that, within the range of reasonable anaesthesia for routine abdominal surgery, different anaesthetic techniques have no obviously different effect on the acute phase protein response whether or not they provide better analgesia, more obvious stress suppression, or merely peripheral suppression of cortisol production. We are interested that, in subsidiary studies on patients undergoing successful renal transplantation, the acute phase protein response was similar to that for cholecystectomy despite the large immunosuppressive doses of exogenous steroids.

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INCIDENCE AND SEVERITY OF SORE THROAT AFTER OPERATION: INFLUENCE OF TRACHEAL TUBE SIZE

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Short term tracheal intubation with cuffed tubes is followed by sore throat and hoarseness in 24–65% of patients. Factors involved include the properties of the tube material [1], cuff design and intracuff pressure [2] and intermittent suxamethonium [3]. We here report a prospective study of sequelae following intubation in fit patients having abdominal or limb operations.

A history of acute coryza, recent sore throat and difficult intubation excluded patients from the study. Patients in all groups were broadly comparable with respect to age, weight and intubation time. Anaesthesia was with thiopentone, suxamethonium and halothane; half the patients had vecuronium and IPPV. In random order women were intubated under direct vision (Macintosh laryngoscope) with either 7- or 8-mm i.d. high volume–low pressure cuffed oral tubes (Franklin) lubricated with water soluble bacteriostatic jelly (KY): 8- or 9-mm tubes were used for men. Cuffs were inflated with room air to 2.5–3 kPa. A sterile disposable oral plastic airway was used in every patient. At the end of operation cuffs were deflated and extubation performed after careful suction of the oral cavity.

When visited 24–36 h after operation by an anaesthetist unaware of the tube used, patients were asked if they had any pain or discomfort since operation. Severity of throat pain was graded as 0, +(mild), ++(severe).

Ten of the 11 patients with a sore throat had been intubated with the larger tube (table IX)—a highly significant finding ($P = 0.00375$) The larger tubes caused significantly more sore throats than the smaller ones in men ($P = 0.025$), but the differences in women was not significant ($P = 0.084$).

TABLE IX. *Frequency and severity of sore throat*

	n	Tube size	Mean intubation time (min) ± SD	Sore throat +	Sore throat ++
Men	27	8	53.1 ± 13.93	0	0
	27	9	54.0 ± 19.02	2	3
Women	27	7	53.4 ± 12.35	1	0
	27	8	55.9 ± 18.32	2	3

Tracheal intubation with tubes having a relatively small diameter significantly reduces the incidence of postoperative sore throat in male patients.

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COMPARISON OF THREE COMMERCIALLY AVAILABLE PREPARATIONS OF SODA-LIME

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Three preparations of soda-lime (Durasorb (MIE Ltd); Viosorb (MIE Ltd); Dragersorb (Drager Medical)) were tested *in vitro* using the new Ohmeda Mk V absorber, to compare carbon dioxide absorbing capacity, clarity and reliability of indicators and cost.

An artificial lung was ventilated in a circle system with a fresh gas inflow of 1050 ml min^{-1} (oxygen 700 ml from the anaesthetic machine, carbon dioxide 350 ml introduced at the patient connection). Gas in the expiratory limb was humidified using a Cape humidifier. The Ohmeda Mk V absorber was filled alternately with 900 g and 1800 g of each soda-lime. Three tests of each agent were made at each weight.

A Datascope Accucap measured carbon dioxide concentrations at the inspiratory limb.

Times to breakthrough, 0.5% and 1% carbon dioxide are summarized in table X.

Durasorb (Mimosa Z, pink to colourless) was the most reliable at indicating exhaustion at 1.0% carbon dioxide (approx. 75% change along cannister height with 1800 g), but produced the least obvious colour change. Viosorb, Dragersorb (ethyl violet, colourless to violet) produced an obvious colour change, but the dye was eluted from the granules at the top of the cannister. It moved downwards, giving the false impression that the soda-lime above was still absorbing, despite its being completely exhausted. Neither indicator reliably demonstrated 0.5% carbon dioxide breakthrough.

Dragersorb exhibited less caking than the other agents. It also tended to give a longer absorbing time than the others under the same conditions. It cost three times as much.

TABLE X. *Mean (range) times (h) to breakthrough, 0.5% and 1% carbon dioxide*

	Breakthrough	0.5%	1%
900 g Durasorb	4.0 (3.8–4.4)	5.4 (5.0–6.0)	6.3 (6.0–7.0)
Viosorb	4.4 (3.4–5.6)	5.5 (4.4–6.8)	6.2 (5.0–7.4)
Dragersorb	4.7 (4.6–4.8)	6.1 (6.0–6.4)	6.8 (6.6–7.0)
1800 g Durasorb	10.7 (9.2–11.6)	13.1 (11.4–14)	14.2 (12.2–15.2)
Viosorb	11.2 (10.0–12)	13.3 (11.2–15)	15.2 (14.0–16.6)
Dragersorb	13.6 (11.6–15.2)	15.2 (14.2–16.4)	15.9 (14.8–16.6)

The indicators tested do not enable the most economical or safe use of soda-lime, and we recommend that little reliance is placed on them. The degree of elution of ethyl violet could make its use in clinical practice unsafe. Capnography is the only certain method of reliably detecting soda-lime exhaustion.

Eighteen hundred grams of either soda-lime safely provides carbon dioxide absorption for at least 9 h.

CHANGES IN PHOSPHOLIPID MONOLAYERS PRODUCED BY GENERAL ANAESTHETICS ARE PARTIALLY INHIBITED BY PIRACETAM

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A mechanism by which anaesthetics might exert their effect is by altering the ionic permeability and therefore the electrical conductance of cell membranes. We studied the effect of isoflurane and enflurane alone or preceded by piracetam 10 µl on the surface potential of the phosphatidylcholine monolayer.

The monolayer was prepared in a Teflon trough (3.15 × 3.75 cm surface area) over potassium chloride 145 mmol litre^{-1}. The surface potential was measured with a Kiethley electrometer. The high input impedence of it was connected to an Americium 241 electrode positioned over the trough. The earthed low impedence input was connected to a calomel reference electrode which was inserted in the trough. The trough and the electrodes were electrically shielded in a brass box. All the experiments were carried out at 28 °C. The surface potential obtained with the potassium chloride was −420 mV. The addition of 30 µl of phosphatidylcholine 1 mmol litre^{-1}, prepared in petroleum ether, produced a positive-going change in the surface potential of the order 420–430 mV. Isoflurane or enflurane 10, 20 and 30 µl were added over the lipid monolayer and the changes in surface potential were recorded. All the experiments were repeated in the same way except that, before the anaesthetic, piracetam 10 µl was added to the trough. Each experiment for a predetermined concentration was repeated three times and the mean value of the changes in surface potential produced by the anaesthetic was calculated (table XI).

The changes produced in surface potential of the PC monolayer were partially inhibited when the anaesthetic was preceded by piracetam 10 µl. Since anaesthetics fluidize the membranes [1] and piracetam opposes this action, piracetam might have an effect on MAC or on recovery time after anaesthesia. MAC of halothane in rats did not change significantly when piracetam was injected during the anaesthetic [2]. Humans pretreated with piracetam showed a shorter recovery period after neurosurgery [3]. Perhaps the time of administration (before or during the anaesthetic) may account for these differences.

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EFFECT OF ADRENALINE ON PLACENTAL TRANSFER OF BUPIVACAINE IN RABBITS

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Adrenaline may reduce intervillous blood flow [1]. Reynolds and Taylor [2] demonstrated increased fetal:maternal ratios of bupivacaine associated with adrenaline, but this is not a consistent finding [3]. We studied the effect of adrenaline on placental transfer of bupivacaine in rabbits.

Pregnant, anaesthetized rabbits received an i.v. infusion of bupivacaine 1.25 mg ml^{-1}, either plain ($n = 8$) or with adrenaline 1.25 µg ml^{-1} ($n = 8$). Fetuses were removed at 15-min intervals and simultaneous samples of maternal arterial plasma and mixed fetal plasma obtained. Bupivacaine concentrations were measured on all samples, by gas chromatography. Significant differences were tested using analysis of variance and a nested analysis of covariance.

There were no significant differences in blood-gas tensions, mean arterial pressures, maternal arterial (M) or fetal plasma (F) concentrations of bupivacaine between the two groups. F:M ratios were not significantly higher in the adrenaline group (fig. 3).

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TABLE XI. *Changes in surface potential (mV) of phosphatidylcholine monolayer produced by isoflurane (Iso.) or enflurane (Enf.) alone or preceded by piracetam (PI)*

Amount of anaesthetic	Isoflurane	Iso. ± PI	Enflurane	Enf. + PI
10 µl	105 ± 0.6	75 ± 0	65 ± 0.6	62 ± 0.6
20 µl	110 ± 0	86 ± 1.5	75 ± 0.6	70 ± 0.6
30 µl	120 ± 0	92 ± 1.2	92 ± 0.6	86 ± 1.2

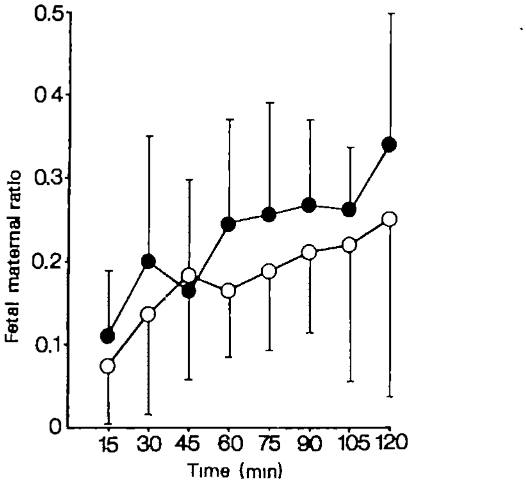

FIG. 3. Fetal:maternal bupivacaine concentration ratios (mean ± SD) after administration of bupivacaine 1.25 mg ml^{-1} plain (○) or with adrenaline 1.25 µg ml^{-1} (●).

CHANGES IN BLOOD VOLUME DISTRIBUTION ASSOCIATED WITH GENERAL ANAESTHESIA

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An increase in the volume of blood within the thorax and abdomen has been suggested to explain the reduction in lung volume associated with general anaesthesia, despite constant external dimensions [1]. However, when blood volume within the trunk is increased experimentally, so that lung volume is reduced, the dimensions of the ribcage increase [2]. We have assessed the effects of general anaesthesia on blood volume by a direct method using radioisotope labelling.

Five male volunteer subjects gave consent for the study, which had ethics committee approval. The subjects lay on a mobile scanning table with their arms by their sides, encased in lead shields so that labelled blood in the arms was not detected. The table moved so that the subject passed from foot to head between horizontal collimated detectors placed above and below the table, as activity in successive transverse "slices" of the subject was measured After the patient had rested on the table for 15 min, albumin labelled with 80 MBq of TC^{99} was given i.v., and duplicate scans performed 10 min later, during stable anaesthesia with 1% halothane and 67% nitrous oxide in oxygen and after recovery. Counts obtained were corrected for decay, averaged, and summed into those obtained from the legs (up to 20 cm caudal to iliac crest), abdomen (iliac crest to 4 cm cephalad to xiphisternum), ribcage (4 cm cephalad to xiphisternum to 2 cm cephalad to suprasternal notch) and head (above ribcage). The counts were compared with the preceding period by paired *t* test.

Leg counts increased and abdomen counts decreased in all subjects on induction of anaesthesia (both $P < 0.05$) (table XII). Ribcage counts did not change significantly. On recovery, activity increased significantly in both ribcage and abdomen (both $P < 0.05$), but the decrease in leg counts was not significant.

TABLE XII. *Mean (SD) counts, in the different time periods, and mean changes between periods*

	Leg	Abdomen	Ribcage	Head
A: Before anaesthesia	71022 (5816)	48607 (9263)	36448 (6447)	32616 (4252)
B: Anaesthesia	78788 (9584)	47287 (8229)	36414 (6720)	34552 (3662)
C: After anaesthesia	75388 (5929)	51427 (8435)	37869 (6302)	34191 (4481)
B−A	+7767 (5291)	−1137 (1116)	−34 (720)	+1936 (2363)
C−B	−3400 (5215)	+4140 (1540)	+1455 (995)	−361 (2308)

The preliminary findings of this study do not support the hypothesis that blood moves into the trunk during general anaesthesia to contribute to a reduction in FRC.

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OPERATING THEATRE POLLUTION IN GLASGOW

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Surveys of personnel exposure to nitrous oxide have been carried out in six Glasgow hospitals, using diffusive samplers. Every theatre in each hospital was surveyed for at least 1 week, with samplers being worn by the anaesthetist, circulating nurse and operating department assistant (ODA) or anaesthetic nurse. A fresh sampler was worn for each operating session and the exposures were measured as a time-weighted average for the duration of the session for each person surveyed. Scavenging was available in all of the theatres surveyed.

In all the hospitals, the anaesthetist almost always received a higher exposure than the other staff surveyed. The results from the 17 operating theatres in the Western Infirmary and Gartnavel General Hospital are summarized in table XIII. The measured exposures are compared with a target of 100 p.p.m., which is the statutory limit for an 8-h time-weighted average exposure in Sweden.

TABLE XIII. *Exposure to nitrous oxide in the operating theatre*

	Anaesthetist	Nurse	ODA
n	100	100	84
N_2O exposure (p.p.m.)			
Mean (SD)	171 (211)	46 (48)	60 (53)
Range	16–1590	3–335	4–345
No. > 100 p.p.m.	50 (50%)	11 (11%)	12 (14%)

In three of the other hospitals surveyed, the exposures were markedly greater than those shown above; for example, the mean anaesthetist's exposure ranged from 312 to 625 p.p.m. and the number of anaesthetists' exposures greater than 100 p.p.m. from 80% to 91%. In two of these hospitals (Royal Hospital for Sick Children and Dental Hospital), the increased pollution could be attributed to the difficulty in carrying out effective scavenging for the typical procedures in these hospitals. In the third (Southern General Hospital), the operating theatres are older and perhaps less well ventilated than those in the other hospitals. In the Southern General Hospital and the Royal Hospital for Sick Children, the anaesthetic nurse received an exposure of greater than 100 p.p.m. on 47% and 67% of the sampling periods, respectively. The Institute of Neurological Sciences, in which a typical operating list consisted of one or two long procedures, produced the lowest exposures of all the hospitals surveyed, with the mean anaesthetist's exposure being 97 p.p.m. and the number of anaesthetists' exposures in excess of 100 p.p.m. being 31%.

Some of the exposures found in these surveys seem undesirably high, and investigations are currently in progress of possible causes of these high exposures. Preliminary findings suggest that a considerable part of the exposure arises in the anaesthetic room, where it is often difficult to carry out effective scavenging.

CARBON DIOXIDE PRODUCTION AND VENTILATORY EFFICIENCY DURING CONTROLLED VENTILATION IN CHILDREN WITH CYANOTIC HEART DISEASE

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Children who are cyanotic because of right-to-left intracardiac shunting also have an increased physiological deadspace,—that is, reduced ventilatory efficiency. However, metabolism is depressed in chronic severe hypoxaemia [1], and therefore tissue carbon dioxide production should also be reduced. This paper examines these aspects of gas exchange in cyanotic children, and compares them with the findings in acyanotic ones.

Thirty-four children (15 cyanotic and 19 acyanotic were anaesthetized for cardiac surgery with nitrous oxide and fentanyl. Carbon dioxide elimination ($\dot{V}CO_2$) and the physiological deadspace:tidal volume ratio, V_D^{phys}/V_T, were measured using a computerized on-line system based on the Servo ventilator [2]. Measurements were made with the child in the supine position during undisturbed anaesthesia, at least 30 min after induction, when steady state was obtained,—that is, when production and elimination of carbon dioxide were equal.

At an $F_{I_{O_2}}$ of 0.5, group mena Pa_{O_2} values were 7.4 and 28.5 kPa in cyanotic and acyanotic children, respectively. Mean body weights were 9.1 and 11.8 kg ($P = 0.06$), and mean oesophageal temperatures were 36.2 and 36.3 °C. Mean end-tidal P_{CO_2} values were 3.8 and 3.9 kPa, mean Pa_{CO_2} were 4.8 and 4.0 kPa. The relationship between carbon dioxide production (y) (ml min^{-1}) and body weight (kg) (x) was:

cyanotic: $y = 24 + 4.29x$, $r = 0.92$;
acyanotic: $y = 35 + 5.17x$, $r = 0.91$.

The two regressions are significantly different ($P < 0.01$). $\dot{V}CO_2$ was thus about 20% lower in cyanotic children. Mean V_D^{phys}/V_T values were 0.41 (cyanotic) and 0.25 (acyanotic); ventilatory efficiencies ($1 - V_D^{phys}/V_T$) were therefore 0.59 and 0.75, that is also about 20% lower in cyanotic children.

Ideally, expired carbon dioxide should be monitored during anaesthesia in all children with cardiac disease. Children with right-to-left shunts have arterial–end tidal P_{CO_2} differences of 0.3–2.0 kPa, so that acceptable ventilation will be obtained if end-tidal P_{CO_2} is kept to about 4.0 kPa. If expired carbon dioxide monitoring is not available, then a ventilation nomogram must be followed. The implication of the present study is that cyanotic children, although they have a mean reduction in ventilatory efficiency of 20% compared with acyanotic children, also produce 20% less carbon dioxide and therefore a "normal" ventilator setting should give an adequate Pa_{CO_2}.

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CHANGES IN PALMAR EVAPORATIVE WATER LOSS DURING ANAESTHESIA: THE INFLUENCE OF DIFFERENT PREMEDICANT DRUGS

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Measurement of palmar sweat is becoming established as a quantitative method of measurement of anxiety [1, 2]. Premedicant drugs are frequently administered to patients about to undergo surgery and may influence measurements of palmar sweat either by attenuating the central response to noxious stimuli, or by interfering peripherally with palmar sweat production.

Accordingly this was studied in 79 patients who were scheduled to undergo routine cystoscopy and who were randomly allocated on a double-blind basis to one of four premedication groups: lorazepam 2 mg by mouth (group 1), hyoscine 0.2 mg i.m. (group 2), papaveretum 10 mg i.m. (group 3), and combined papaveretum 10 mg and hyoscine 0.2 mg i.m. (group 4). Patients aged older than 75 yr were excluded from the trial.

As shown in figure 4; palmar sweat measurements were recorded on the day before surgery (event 1), on arrival in the anaesthetic room (event 2), and repeatedly during induction of anaesthesia (events 3–5) and subsequent surgery (events 6 and 7). Heart rate was recorded simultaneously with palmar sweat measurement. In addition, on the day before surgery and on arrival in the anaesthetic room, patients were asked to mark a 10-cm line as a linear analogue scale for subjective assessment of their anxiety.

Initial measurements of palmar sweat, heart rate and linear analogue score were similar for all four groups. Subsequent palmar sweat measurements demonstrated significant differences between group 1 and groups 3 and 4. In contrast, there was no difference between groups for change in linear analogue score or heart rate.

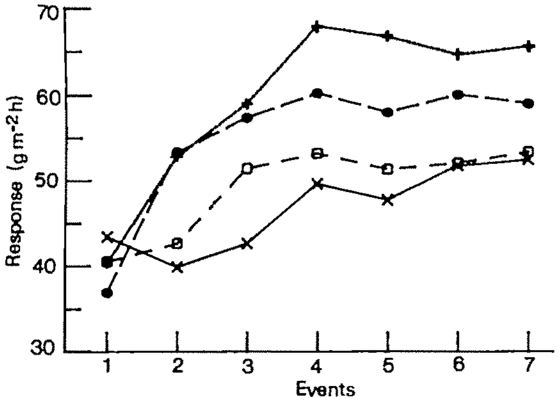

FIG. 4. Mean palmar sweat responses for each of the four groups. + = Group 1 ($n = 20$); ● = group 2 ($n = 19$); ○ = group 3 ($n = 21$); × = group 4 ($n = 19$).

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EFFECT OF DICLOFENAC AND NEFOPAM ON THE POSTOPERATIVE MORPHINE DEMAND FROM A PATIENT CONTROLLED ANALGESIA APPARATUS

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Pain relief following major surgery is usually achieved with parenteral opioids. The addition of a second non-opioid drug may lessen the opioid demand and consequently their unwanted effects (the opioid sparing effect).

We have used the Cardiff Palliator Patient Controlled analgesia apparatus delivering morphine to investigate any opioid sparing effect of diclofenac and nefopam following major lower abdominal surgery.

Following hospital Ethical Committee approval and written informed consent, women of ASA class I or II were randomly allocated to a control group, a group to receive nefopam 20 mg i.m. or a group to receive diclofenac 75 mg i.m. At the preoperative visit the Cardiff Palliator was explained and demonstrated. Apart from the avoidance of regional or local anaesthetic techniques no attempt was made to control the type of anaesthesia administered. However, all subjects received nitrous oxide, oxygen, an opioid and a neuromuscular blocking drug with or without a volatile supplement. About 15 min before antagonism of the non-depolarizing neuromuscular blocker, the trial drug was injected i.m.

In the recovery room the Cardiff Palliator was connected via a one-way valve to the i.v. cannula. It was set to deliver a 3-mg bolus of morphine with a lock out time of 5 min. The total dose of morphine administered after 24 h was recorded and the patient asked to complete a linear analogue pain score of her impression of her pain over the preceeding 24 h.

TABLE XIV. *Details of patients, duration of anaesthesia requirement for morphine and subjective pain scores (mean values ± SD)*

	Control ($n = 14$)	Nefopam ($n = 14$)	Diclofenac ($n = 14$)
Age (yr)	37.8 (7.3)	42 (7.1)	39.9 (6.5)
Weight (kg)	65.7 (8.7)	71 (10.6)	67.5 (13.5)
Duration of anaesthesia (min)	86.4 (27)	71 (11.7)	83 (24)
24-h dose of morphine (mg)	59.2 (31)	60.5 (22)	51 (15.8)
24-h pain score (mm)	40.5 (19.7)	44 (18.3)	39.2 (19)

The results are indicated in table XIV. No statistically significant differences were observed. Single doses of diclofenac 75 mg or nefopam 20 mg given before recovery did not have a morphine-sparing effect in this study. This contrasts with the findings of Derbyshire and Richardson [1], that diclofenac administered by mouth and rectally reduced the amount of morphine required by the patient in the first 12 h after surgery.

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RESPIRATORY FUNCTION AFTER OESOPHAGEAL SCLEROTHERAPY

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Acute respiratory failure has been reported after injection sclerotherapy for oesophageal varices [1]. Corbett, Taylor and Shields [2] showed that i.v. administration of 20 ml of the sclerosants ethanolamine oleate or sodium tetradecyl sulphate in sheep resulted in an increase in extravascular lung water and a significant decrease in arterial Po_2 (Pa_{O_2}). Karacagil and colleagues [3] demonstrated that i.v. administration of ethanolamine oleate 0.5 ml kg^{-1} in rabbits produced a decrease in the circulating concentrations of leucocytes and platelets with sequestration of platelets in the kidney, liver and lung. They proposed that organ dysfunction after injection sclerotherapy was the result of blood cell microembolization. A study was therefore undertaken to determine whether elective injection sclerotherapy for oesophageal varices resulted in any deterioration in respiratory function.

Arterial Po_2, Pa_{CO_2} and vital capacity (VC) were measured before and 1 day after operation in 11 patients receiving elective injection sclerotherapy under general anaesthesia on a total of 15 occasions. A control comprised five patients who underwent oesophagogastroscopy on six occasions, but did not receive injection sclerotherapy. On a further 14 occasions blood leucocyte and platelet concentrations were measured in 12 patients undergoing sclerotherapy. Blood was taken before operation, immediately after the injection, 5 min after injection and 60 min after injection. The same measurements were made in a control group of six patients who were anaesthetized and with an oesophagoscope inserted, but who did not receive an injection.

In patients who received injection sclerotherapy Pa_{O_2} decreased by 6.2(+2.8)mm Hg (ns) after operation but increased by 3.4(+1.9)mm Hg (ns) in patients who did not. The difference between the two groups was significant ($P < 0.05$). Vital capacity decreased by 0.27 litre ($P < 0.02$) in patients injected with ethanolamine oleate, but did not alter in those who underwent oesophagogastroscopy. In the patients who received injection sclerotherapy there was a significant correlation between the change in Pa_{O_2} and the decrease in VC ($r = 0.787$) ($P < 0.001$). No such relationship existed in the group that was not injected. Blood leucocyte and platelet concentrations did not alter in either the injected or the non-injected group at the times studied.

These results suggest that elective injection sclerotherapy of oesophageal varices under general anaesthesia is associated with a deterioration in respiratory function, namely a decrease in Pa_{O_2} and in vital capacity. These findings are not accompanied by any change in circulating leucocyte or platelets and may be occurring secondary to sclerosant embolizing to the lung.

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DIFFERENTIAL NERVE BLOCKADE: THE AMINO-ACYL-AMIDES

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Previous studies [1] of the *in vitro* nerve blocking activity of both amino-ester and amino-amide type local anaesthetic drugs have shown that the ester linked compounds are inherently more potent than the amide-linked agents. It has also been shown that the rate at which equipotent concentrations of the drugs block A fibres relative to C fibres is dependent on the lipid solubility and pKa of the agent. A third group of compounds—the amino-acyl-amides—is in clinical use and the present study was undertaken both to find out how their activity relates to the other drugs, and to compare a new member of the class—ropivacaine—with the two older drugs, bupivacaine and mepivacaine.

The cervical portions of the vagus nerves of non-pregnant female albino rabbits were desheathed and placed in an air-tight three-section chamber which was maintained at 37 °C. The outer sections contained stimulating and recording electrodes and the central portion was perfused with a carbonated-Liley solution. The compound action potential signal was amplified, digitized and then recorded using a micro-computer system. The nerves were stimulated at 0.0167 Hz and, after an initial stabilization period, were perfused with a submaximally blocking concentration of one of the test agents. By plotting the percentage decrease in the action potential heights (probit scale) against log drug concentration, dose–response relationships were established from which the ED_{50} for the effect of each drug on each fibre type was obtained. These results are shown in table XV.

TABLE XV. *ED_{50} (mmol) for three drugs*

	Fibre type		
	A	B	C
Mepivacaine	0.190	0.242	0.492
Ropivacaine	0.034	0.050	0.092
Bupivacaine	0.026	0.038	0.054

The calculated lipid solubilities of the agents correlated well with these indicators of potency, but there were no obvious differences between the agents in the relative rates at which they blocked different fibre types. Comparison of these figures with equivalent data for amino-amide drugs suggests that the amino-acyl-amide structure is inherently less potent.

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INFLUENCE OF NITROUS OXIDE INHALATION ON SELECTED PHYSIOLOGICAL RESPONSES TO EXERCISE

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Six healthy men breathed either 10% nitrous oxide or air during a 20-min exercise period at 40% of maximal aerobic

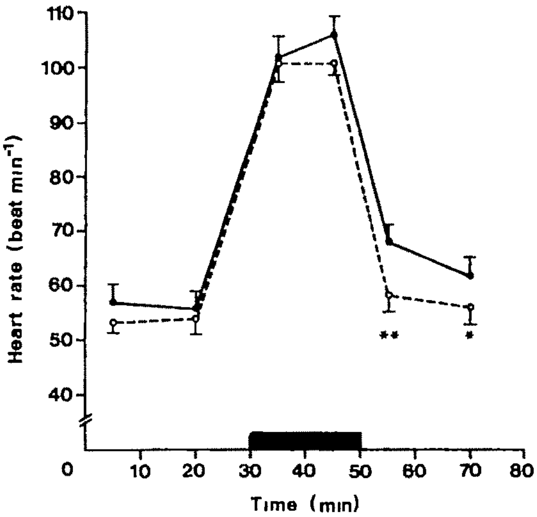

FIG. 5. Heart rates (mean ± SEM) when air (closed circles) or nitrous oxide (open circles) was breathed during the exercise period (black bar). Significant differences: $^{**}P < 0.02$; $^{*}P < 0.05$.

capacity. Various physiological measurements were made during the study. Nitrous oxide caused no significant differences at any time in oxygen consumption, sweat production rate, blood lactate, pyruvate or free fatty acid concentrations. However, the heart rate was significantly reduced for at least 20 min in the recovery period after breathing nitrous oxide during exercise (fig. 5). In a further experiment two subjects exercised for 1 h at the same rate and inhalation of nitrous oxide altered the pattern of sweat production.

LOW-FLOW NITROUS OXIDE–OXYGEN AND NITROGEN–OXYGEN CIRCLE SYSTEMS: EFFECTS OF BODY SIZE

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This presentation is a further examination of data obtained during an investigation of the behaviour of circle breathing systems using either 50 % nitrogen in oxygen or 50 % nitrous oxide in oxygen (random allocation) as fresh gas [1].

Patients undergoing elective general surgical procedures either breathed spontaneously or received artificial ventilation from a circle system with fresh gas flow (FGF) 4 litre min^{-1} for 10 min and thereafter 1 litre min^{-1}. Concentrations of oxygen in the expiratory limb of the breathing system were measured at 5-min intervals and recorded. Fat free mass was estimated from body weight and measurements of skinfold thickness [2].

As previously reported the oxygen concentration decreased from 39.9 % (mean; range 31–39, $n = 197$) and 45.6 (36–51, $n = 195$) 5 min after reducing FGF to 32.0 (24–39, $n = 54$) and 38.4 (28–45, $n = 72$) over the next 60 min in the nitrogen–oxygen and nitrous oxide–oxygen groups, respectively. At individual times the oxygen concentration was significantly related inversely to bodyweight and more strongly to fat free mass; these relationships were steeper in the nitrogen–oxygen group than in the nitrous oxide–oxygen group at each time. The slope of the relationship between oxygen concentration and fat free mass reached an early plateau in the nitrogen–oxygen group, but continued to become steeper over the period of observation in the nitrous oxide–oxygen group.

Over the durations of anaesthesia studied here, the presence of nitrous oxide in low-flow systems reduces the dependence of oxygen concentration on fat free mass and body weight.

ACKNOWLEDGEMENT

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EFFECT OF NICARDIPINE ON GLUTATHIONE S-TRANSFERASE RELEASE FOLLOWING HALOTHANE ANAESTHESIA

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Plasma concentrations of hepatic glutathione S-transferase (GST) increase transiently after anaesthesia with halothane, but not after isoflurane [1]. Studies in rats suggest that the calcium antagonist nicardipine reduces the degree of experimentally-induced hepatic damage. We tested the possibility that nicardipine had a hepato-protective effect in association with halothane anaesthesia in man, in a parallel, placebo-controlled, randomized trial.

Eighty patients of ASA class I and II, aged 18–70 yr, undergoing elective orthopaedic surgery were studied. Patients who had undergone halothane anaesthesia within 3 months were not eligible. An exponentially decreasing infusion of either nicardipine 50 mg ($n = 42$) or normal saline ($n = 38$) was commenced 1 h before induction of anaesthesia and continued for 6 h. Arterial pressure was measured throughout the infusion and the infusion was discontinued if the systolic pressure became less than 75 % of the preinfusion value.

Premedication was with temazepam by mouth. Anaesthesia was induced using thiopentone 4–6 mg kg^{-1} and maintained with 66 % nitrous oxide and halothane. Suxamethonium 1 mg kg^{-1} was administered to facilitate tracheal intubation if this was necessary. All patients breathed spontaneously. End-tidal carbon dioxide and halothane concentrations were recorded every 5 min and mean values for each patient determined. Samples for GST assay were taken before commencing the infusion and at 1, 3, 6 and 24 h after induction.

Data were not analysed from patients who had abnormal liver function tests before operation (including GST) or whose end-tidal carbon dioxide concentration exceeded 8 kPa. Groups were compared using the Wilcoxon two-sample test; temporal changes in GST from the preoperative value with the Friedman test; and correlation of GST changes and duration of anaesthesia by Spearman's rank test.

Mean end-tidal halothane concentration was similar in the two groups (placebo 1.1 %, nicardipine 1.0 %). The group receiving nicardipine had longer durations of anaesthesia (mean 54 min compared with the 39 min; $P < 0.01$). However, there was no correlation between the magnitude of change in GST at 3 and 6 h and duration of anaesthesia. GST increased significantly at 3 and 6 h after induction in both groups. The decrease at 24 h in the nicardipine group was also statistically significant (table XVI). Nicardipine did not influence the magnitude of the increase in GST at 3 or 6 h.

The results obtained confirm that halothane anaesthesia causes a transient release of GST and that nicardipine does not significantly prevent such release.

TABLE XVI. *Medians of GST values* (μg litre^{-1}) *for patients receiving placebo and nicardipine infusion in association with halothane anaesthesia.* *$P < 0.05$; **$P < 0.01$

	Pre	1	3	6	24
Placebo	2.2	2.1	2.7**	2.8**	2.0
Nicardipine	2.4	2.0	2.9**	2.5*	1.7*

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COMPARISON OF TRIMETAPHAN NITROPRUSSIDE AND SODIUM NITROPRUSSIDE IN GREYHOUNDS

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Trimetaphan nitroprusside (TNP) is a new potent hypotensive agent intended to induce decreases in arterial pressure unaccompanied by the development of resistance. It combines one ion of nitroprusside with two of trimetaphan, and was developed following the work of MacRae, Wildsmith and Dale [1], who showed that a mixture of these two separate drugs produced satisfactory hypotension in anaesthetized patients. We have investigated the dose–response characteristics of TNP in anaesthetized greyhounds and compared its hypotensive properties with those of sodium nitroprusside (SNP).

Greyhounds were anaesthetized with thiopentone 25 mg kg^{-1}, alpha-chloralose 40 mg kg^{-1} bolus, then 10 mg kg^{-1} every 2 h and phenoperidine 1-mg bolus, then 1-mg h^{-1} infusion, and mechanically ventilated with 30% oxygen in nitrous oxide. The dose–response to TNP was obtained in five dogs by measuring the haemodynamic changes during progressively increasing infusion rates. A further six dogs received alternate infusions of SNP and TNP in a randomized manner sufficient to reduce mean arterial pressure by 30% over a period of 30 min. A rest period of 2 h always separated SNP and TNP infusions. Haemodynamic changes were measured and the total doses used were calculated for subsequent comparison. Plasma cyanide concentrations were measured before and after the drug infusions using an automated technique [2].

The dose–response results indicate that TNP caused a predictable decrease in mean arterial pressure accompanied by a moderate but variable increase in heart rate, but no significant change in cardiac output. In the second part of the study the results show that both SNP and TNP had similar properties when infused to our model. In fact, for the same degrees of hypotension, tachycardia was greater with the new agent, but SNP increased cardiac output more than TNP. There was no significant difference between the doses of each drug used, and neither increased plasma cyanide concentrations to potentially dangerous values.

We conclude that although TNP causes predictable hypotension in the greyhound it may cause severe tachycardia and therefore possesses no appreciable advantage over SNP.

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AUDITORY EVOKED RESPONSE IN ANAESTHESIA: EFFECT OF NITROUS OXIDE

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Studies on volatile anaesthetic agents [1, 2] showed graded changes in the amplitude of the early cortical waves, Pa and Nb of the auditory evoked response (AER), related to the end-tidal concentration. These studies were conducted between induction and surgery, and used nitrous oxide in oxygen as the carrier gas. The AER (nitrous oxide–oxygen alone) showed high amplitudes of Pa and Nb which were attenuated subsequently by increasing volatile concentration. It is necessary to show if these high amplitudes are a result of prior intubation, or a special characteristic of nitrous oxide anaesthesia.

The effects of nitrous oxide or isoflurane in oxygen were compared in eight surgical patients (ASA I and II, aged 38–49 yr), premedicated with papaveretum and hyoscine, or morphine and atropine. Anaesthesia was induced with thiopentone 2–4 mg kg^{-1} and pancuronium or vecuronium 0.1 mg kg^{-1} for intubation. Patients were ventilated ($P\text{E}'_{CO_2}$ 4.5–5.0 kPa) with isoflurane or nitrous oxide in oxygen. Inspired concentrations were adjusted manually to produce end-tidal concentrations of 0.65–0.75% or 60–65%, respectively (0.6 MAC) measured by mass spectrometer, in three blocks of 10 min according to the cross-over sequence in table XVII, used to test for a possible effect of prior treatment or drugs. The AER was analysed as previously described using the average of the last 2048 clicks (5.7 min) of each block, during which period end-tidal values were stable, and residual gases had declined to < 5% of the previous value.

TABLE XVII. *Mean Pa amplitudes* (μV). *N = Nitrous oxide; I = isoflurane*

Period (min)	Group 1	Group 2	Group 3	Group 4
1–10	0.18(I)	1.34(N)	0.57(I)	1.12(N)
11–20	0.63(N)	0.22(N)	0.51(N)	0.23(I)
21–30	0.67(N)	0.60(N)	0.23(I)	0.37(I)

Analysis of variance demonstrated significant reduction in the amplitudes of Pa ($P < 0.001$) and Nb ($P < 0.003$) for isoflurane with respect to nitrous oxide at 0.6 MAC in all of the blocks. No relationship between the drug and period effects was found, but amplitudes were higher in the 10 min following intubation ($P < 0.01$) than subsequently, presumably as a result of stress.

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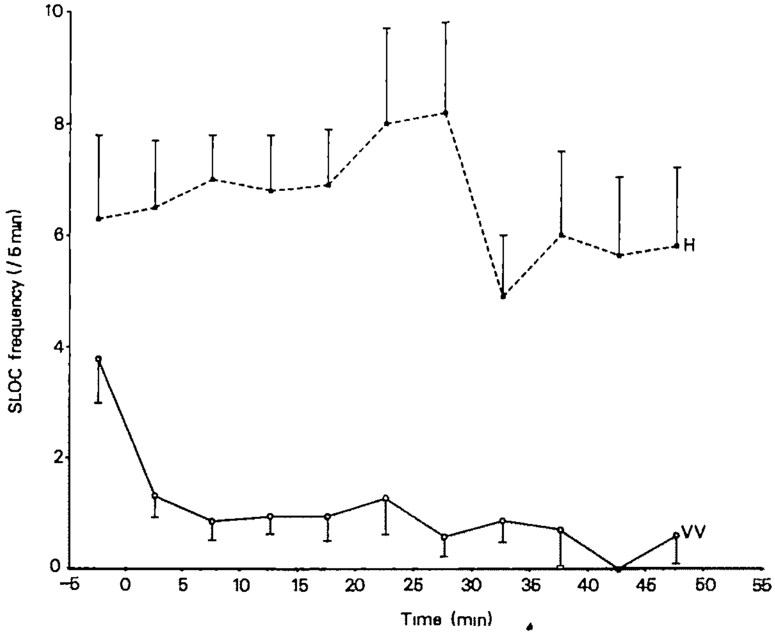

FIG. 6. Spontaneous lower oesophageal contraction (SLOC) frequency in patients undergoing hysterectomy (H) or varicose vein surgery (VV).

RELATIONSHIP BETWEEN LOWER OESOPHAGEAL CONTRACTILITY AND LEVEL OF SURGICAL STIMULATION

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Spontaneous oesophageal contractions are known to be related to stress [1]. An oesophageal contractility monitor has recently been developed for use in the anaesthetized subject. Spontaneous lower oesophageal contractions (SLOC) are sensed by a water-filled balloon positioned in the lower third of the oesophagus, and inflation of a more proximal air-filled balloon can initiate secondary, provoked lower oesophageal contractions (PLOC). Early work suggested that oesophageal activity is suppressed by volatile or i.v. anaesthetic agents and by opioids [2]. However, adequacy of anaesthesia depends not only upon the amount of anaesthetic agent administered, but also upon the level of surgical stimulation. The present study was designed to discover if, in the presence of identical anaesthetic conditions, oesophageal contractility is related to the level of surgical stimulus.

Forty-four female patients (ASA I or II) scheduled to undergo either hysterectomy or varicose vein surgery were studied. The investigation was approved by the District Ethics Committee, and each patient consented to inclusion. Every patient received premedication of temazepam 20 mg by mouth. Anaesthesia was induced using thiopentone 5 mg kg^{-1} and morphine 10 mg i.v. Neuromuscular blockade was achieved using vecuronium 0.1 mg kg^{-1}, and the lungs were ventilated through a tracheal tube with 66% nitrous oxide in oxygen and 0.5% isoflurane. Supplements of vecuronium 0.025–0.035 mg kg^{-1} were administered as indicated by the appearance of the second twitch on train-of-four ulnar nerve stimulation. Before the start of surgery, an oesophageal probe was positioned with the tip in the lower oesophagus and connected via a pressure transducer to a Lectron 301 oesophageal monitor (Antec Systems Ltd). Fresh gas flow was titrated so that the end-tidal carbon dioxide concentration remained between 4 and 5%, and the concentration of isoflurane was measured continuously. SLOC frequency and PLOC amplitude were recorded for the duration of anaesthesia. The period of monitoring was divided into 5-min epochs starting at the time of incision, and oesophageal activity in the two groups was compared using the Wilcoxon rank sum test.

The 22 patients in each group were comparable in respect of age, weight and mean end-tidal carbon dioxide concentration. Both SLOC frequency and PLOC amplitude were significantly greater ($P < 0.005$) in patients undergoing hysterectomy for all epochs after incision (fig. 6).

This study demonstrates for the first time that oesophageal activity relates, not only to the administration of anaesthetic agents, but also to the magnitude of the surgical stimulus.

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LOWER OESOPHAGEAL CONTRACTIONS AND DEPTH OF ANAESTHESIA AND AWARENESS

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The measurement of lower oesophageal contractions (LOC) as an index of depth of anaesthesia has been demonstrated [1]. The potential for LOC as a guide to impending awareness under anaesthesia has therefore been studied.

Patients, ASA I–III, had an oesophageal probe with a distal sensing balloon and a proximal provoking balloon inserted to the lower oesophagus, either while awake after topical anaesthesia and i.v. diazepam, or after a small dose of propofol. The probe was connected to a pressure transducer and chart recorder (Antec 301, Antec Systems Ltd, Oxford. Recording of spontaneous and provoked (at 1-min intervals) contractions continued as the patients regained consciousness from the light propofol-induced anaesthesia or with the patient awake, and then subsequently during a slow induction by a propofol infusion. The patient's conscious level was tested during emergence and induction by the response to a request to squeeze the investigator's hand. The time at which hand-squeezing appeared or disappeared was noted and called the "cross-over point." All patients were studied before surgery began. Mean frequency and amplitude of spontaneous and provoked contractions, and the mean oesophageal contractility index (OCI) were analysed before and after the cross-over point during 2- and 4-min periods (if available). (The Oesophageal Contractility Index is calculated from 70 (frequency of spontaneous contractions)+(mean amplitude of provoked contractions), and in an empirical formula based upon the original data [1].)

Recordings from the awake state to unconsciousness were made in 17 patients, and from unconsciousness to the awake state in 14 patients. There were increases in the frequency of spontaneous contractions ($P = 0.002$), the peak amplitude of spontaneous contractions ($P = 0.007$), the mean amplitude of spontaneous contractions ($P = 0.017$), the peak amplitude of provoked contractions ($P = 0.006$), and the OCI ($P = 0.002$) as patients regained consciousness. There were decreases in the frequency of spontaneous contractions ($P = 0.001$), the peak amplitude of spontaneous contractions ($P = 0.005$), the mean amplitude of spontaneous contractions ($P = 0.005$), the peak amplitude of provoked contractions ($P = 0.006$), the mean amplitude of provoked contractions ($P = 0.042$), and the OCI ($P = 0.001$) as patients became unconscious.

There were significant changes in the mean frequency and peak amplitudes of spontaneous contractions, and the mean peak amplitudes of provoked contractions as patients emerged from anaesthesia, and became unconscious. In addition there was a significantd change in the OCI. The changes in spontaneous frequency and provoked amplitude support the findings of Evans, Davies and Wise [1] that LOC are related to depth of anaesthesia. However, changes in rate and amplitude of contractions did not occur in every patient, and in some patients the changes were minor only. Also, no particular frequency or amplitude could be identified as signifying a particular depth, or level, of anaesthesia. This may be because there is not, as yet, a standard method of identifying anaesthetic depth, and the presence of absence of response to command is a crude way of determining if a patient is awake.

We conclude, therefore, that monitoring the rate and amplitude of spontaneous contractions, the amplitude of provoked contractions, and calculating the OCI, can relate to the depth of anaesthesia and may be helpful in preventing lightening of anaesthesia in an anaesthetized patient to the point of awareness. Although valuable, inter-patient variability in both rate and amplitude of LOC does not allow detection of awareness in every anaesthetized patient.

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AN APPROACH TO THE MEASUREMENT OF DEPTH OF ANAESTHESIA

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There is increasing interest in measuring the "depth" of anaesthesia and a variety of methods have been proposed. These include measurements of autonomic activity and a variety of methods of processing the EEG with or without added controlled stimuli.

Such methods purport to measure a gradation or continuum of depression of the CNS and the only way of attempting to validate them has been to correlate the measurement of depression with the assumed brain partial pressure of an inhaled general anaesthetic. If the method is to have any credibility, the measurement it gives must correlate with anaesthetic partial pressure. No guidance is given as to where, as the continuum is descended, anaesthesia can be said to begin. A further problem of these methods is that the subject's position in the continuum appears to depend, at least in part, on the presence or absence of (surgical) stimulus.

The oldest method of detecting the existence of the anaesthetic state is the observation of the presence or absence of movement on surgical incision. As a method of assessing anaesthetic "depth" this has a number of merits:

(a) Most anaesthetists would agree that an unparalysed anaesthetized subject who does not move on incision is not "aware" and will not have memory of the event.

(b) The "stimulus affecting 'depth'" problem is circumvented.

(c) The method is the basis of the MAC determination, a concept which has considerable theoretical and experimental support.

Data used to determine MAC can be analysed to measure the distribution (scatter) of the individual anaesthetizing concentrations (IAC) in the population. The proposal is that other methods of measuring anaesthetic "depth" should show a similar or smaller scatter.

Passing down a continuum derived from one of the previously mentioned methods of measuring "depth", a point is reached at which the subject does not respond to incision. Ideally, the concentration of anaesthetic at which this occurs (IAC) should be determined and this would give a fixed point on the continuum. Unfortunately, it is not easy to do this in practice. Instead it is proposed that one, or preferably more, fixed points on the continuum should be defined.

Quantal or graded data could be used to locate points. The scatter of anaesthetic concentrations correlating with the points should be similar to the scatter found in data used for MAC determinations. This proposal will be illustrated by data from observations of oesophageal pressures made during anaesthesia.

POSTER PRESENTATIONS

PRESSURE REVERSAL OF AMPHETAMINE-INDUCED HYPERACTIVITY

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Anaesthesia produced by gaseous and i.v. anaesthetics, and by benzodiazepines, is "reversed" by a hyperbaric environment [1]. On the other hand sedation, as characterized by reduced motor activity produced by benzodiazepines, has been found to be not "reversed" by a hyperbaric environment [2]. THe effects of pressure on an agent such as amphetamine, that produces hyperactivity rather than anaesthesia or sedation, have not been examined.

Locomotor activity was measured, in a pressure chamber, using a pair of activity wheels. In each experiment two female TO mice, one injected i.p. with D-methamphetamine $5\ \text{mg kg}^{-1}$ and the other injected i.p. with the saline drug vehicle, were each enclosed in a separate wheel of the apparatus. The chamber was maintained at 1.3 atmospheres absolute (ATA) or pressurized to 17, 34 or 51 ATA; $Po_2 = 0.4$–0.5 ATA in all experiments. The pressure of 51 ATA was considered the maximum without neurological signs associated with high pressure.

Measurements of activity, in arbitrary units, were started 20 min after injection and maintained for 60 min. The data for both the control and treated animals were determined at 1.3, 17, 34 and 51 ATA. Results (table XVIII) show that pressure did cause the amphetamine-induced increase in locomotor activity to be decreased. At 51 ATA the treated animals had the same level of activity as the control animals.

TABLE XVIII. *Mean locomotor activities (arbitrary units) with standard errors of the mean.* $^{**}P < 0.01$

Total pressure	Treated group	Control group	*n*
1.3 ATA	25.7** (5.3)	14.8 (3.1)	16
51 ATA	12.0 (6.3)	12.3 (4.9)	21

From these data it may be inferred that either: (1) there is pressure reversal of the amphetamine-induced locomotor activity or (2) pressure causes an increase in the metabolism of the drug. The second alternative seems unlikely, since an investigation of a number of drugs [3] gave no evidence for an increase in drug metabolism with the increased pressure.

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SLOW-RELEASE METOCLOPRAMIDE (GASTROBID) IN THE PERIOPERATIVE CARDIAC SURGERY PERIOD

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Sixty-five to 70 per cent of patients undergoing cardiac surgery in our unit suffer from nausea or vomiting with its multifactorial aetiology [1] during the 3 days following surgery. We set out to study the efficacy of slow-release metoclopramide in a randomized double-blind fashion in this group of patients.

Hospital Ethical Committee and National Drugs Advisory Board approval having been obtained, 33 patients scheduled to undergo open heart surgery gave their written informed consent to partake in the trial. They were allocated to receive either 30 mg of slow release metoclopramide 2 h before operation with lorazepam 4 mg as premedication and 12-hourly thereafter for 3 days, or identical placebo tablets at the same time intervals. A standard anaesthetic technique was administered and this included 1.5–2.0 mg of preservative-free morphine intrathecally.

For the duration of the study the patients were assessed three times daily. Episodes and severity of nausea, vomiting, the number of doses of escape anti-emetic (prochlorperazine 12.5 mg) and the investigators' global assessment of the efficacy of the medication were recorded. The Mann–Whitney *U* test was applied to the data.

Three patients did not satisfy the inclusion criteria and three patients did not complete the course of tablets. There were 15 patients in the active and 15 in the placebo groups. At extubation eight (53%) of the placebo group retched or vomited, while only five (33%) of the metoclopramide group did so.

Seventy per cent of the active group experienced no nausea during the recovery period, compared with 43% of the placebo group ($P < 0.05$). The investigator's global assessment of the anti-emetic efficacy found a significant difference in favour of the active treatment ($P < 0.05$).

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APPARATUS FOR MEASUREMENT OF BLOOD LOSS DURING TRANS-URETHRAL SURGERY

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Total blood content in a blood–irrigant mixture is given by the expression:

Volume of mixture × mixture Hb/patient's Hb

This apparatus has been designed to measure these parameters and compute the result automatically.

Irrigating fluid containing blood is collected in a reservoir as it accumulates during surgery and a voltage proportional to volume is obtained by continuous weighing.

A pump keeps the reservoir stirred and also pumps fluid from the reservoir round a loop from which samples are drawn on command through a photometric cell in which the intracellular and extracellular haemoglobin concentration is measured.

The haemoglobin measurement is performed in a thin film cuvette using the principle of dual wavelength photometry. This method of measurement compensates for optical scatter caused by debris.

Patient's whole blood AHb is entered manually.

Upon demand a "read" cycle is initiated, at the end of which the shed blood volume is displayed digitally in litre.

The accuracy of the apparatus was validated by using known dilutions of whole blood and by comparing the measurements made by the apparatus with those obtained using standard laboratory equipment.

SUSTAINED RELEASE ORAL MORPHINE— THE INFLUENCE OF GENERAL ANAESTHESIA

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Drug absorption after administration by mouth takes place mainly in the small intestine and is thus critically dependant on the rate of gastric emptying [1]. The aim of the study was to evaluate the effect of general anaesthesia on the absorption of sustained release morphine sulphate administered by mouth. Ethical Committee approval and informed consent was obtained.

Sixteen males (ASA I) undergoing arthroscopic examination of the knee joint were randomly allocated to one of two treatment groups. Group A were given morphine sulphate 50 mg by mouth 4 h before operation. Group B were given morphine sulphate 50 mg immediately before the induction of general anaesthesia (thiopentone, oxygen, nitrous oxide and enflurane). Blood was drawn, heparinized, centrifuged and frozen to −20 °C within a short period of time for control, 0.5, 1, 1.5, 2, 2.5, 3, 3.5 and 4 h for assay of plasma concentration of morphine using a radioimmunoassay technique. The antiserum cross-reacted with morphine-3-glucuronide by less than 5%. Statistical analysis was with one-way analysis of variance and Student's *t* test.

The two groups were comparable for age, weight and height. The mean peak plasma morphine concentration in group A (267 ± 137 (SD) ng mg^{-1}) did not differ significantly from that in group B (288 ± 197 ng ml^{-1}). The time to maximum concentration (T^{max}) was 2.5 and 3.5 h, respectively, for groups A and B. Statistically significant differences in plasma values were obtained at 1, 1.5, 2 and 2.5 h.

Reilly and Nimmo [2] have demonstrated that gastric emptying is normal shortly after anaesthesia for minor surgery. We have shown, however, that absorption of morphine sulphate is delayed during general anaesthesia with enflurane and nitrous oxide after thiopentone induction.

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SUFENTANIL AS SUPPLEMENT TO NITROUS OXIDE IN OXYGEN ANAESTHESIA

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Most studies to date have investigated sufentanil as an analgesic supplement to anaesthesia in doses of 4–30 $\mu g\ kg^{-1}$. The present investigation compared two doses of sufentanil (low dose: 0.4 $\mu g\ kg^{-1}$; high dose: 1.0 $\mu g\ kg^{-1}$) as supplements to nitrous oxide in oxygen anaesthesia in 20 randomly allocated patients (ASA I or II, aged 26–72 yr) undergoing lower abdominal or body surface surgery. All gave informed consent to the study.

After premedication with diazepam 10 mg by mouth 90 min before surgery, anaesthesia was induced with thiopentone 4 mg kg^{-1}, and neuromuscular blockade achieved with vecuronium 0.1 mg kg^{-1}. The dose of sufentanil was given i.v. over 60 s before laryngoscopy and intubation. Anaesthesia was maintained with 67% nitrous oxide in oxygen. Patients were ventilated to normocapnia; at the end of surgery, residual neuromuscular blockade was antagonized with atropine and neostigmine. Haemodynamic variables (heart rate (HR) and systolic (SAP), diastolic (DAP) and mean arterial pressure (MAP)) were recorded throughout anaesthesia and surgery.

At incision, extubation and at times when anaesthesia was judged to be clinically inadequate (heart rate or arterial pressure > 20% above pre-induction value, sweating, lachrymation, patient movement), blood samples were taken for plasma sufentanil concentrations by radioimmunoassay [1].

Induction of anaesthesia and administration of sufentanil resulted in changes in MAP and HR in both treatment groups. There was a dose related decrease in MAP (−31.9% and −41.3% respectively, $P < 0.001$ *v.* awake; $P < 0.03$ between-group difference), but a similar decrease in HR in both treatment groups (mean: −18.4%, $P < 0.001$ *v.* awake). Similar changes were seen for SAP and DAP. Decreases in MAP greater than 30% occurred in four out of 10 patients in the low dose and nine out of 10 in the high dose group (ns).

Despite higher sufentanil concentrations at incision in the high dose group (0.80 ng ml^{-1} (SD: 0.68) *v.* 0.27 (0.22), $P = 0.01$), there was a 47% increase in MAP ($P = 0.011$) compared with a 21.5% increase (ns) in the low dose group group. HR increased in both groups (+12.8% in the low dose group, and +5.9% in the high dose group; $P = 0.011$ and 0.38, respectively *v.* pre-incision value; $P = 0.1$ between groups).

During surgery, six patients in each group showed signs of inadequate anaesthesia, with volatile supplementation at 28–42 min after initial dosage in the low dose group and 23–62 min in the high dose group. Plasma concentrations at supplementation varied between 0.07 and 0.54 ng ml^{-1}.

Extubation was achieved in 18 out of 20 patients within 8 min of the antagonism of neuromuscular blockade (mean:

4.2 min (2.3)) at sufentanil concentrations between 0.04 and 0.37 ng ml^{-1}. One patient (low dose group) required naloxone to initiate adequate spontaneous ventilation.

Our data show CVS changes and duration of effect similar to those reported by Flacke, Bloor and Kripke [2], but with a low incidence of postoperative ventilatory depression (5% compared with 41%).

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ASSESSMENT OF THE FRESH GAS FLOW REQUIREMENTS OF THE ENCLOSED MAGILL ANAESTHETIC BREATHING SYSTEM DURING SPONTANEOUS VENTILATION

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The Enclosed Magill anaesthetic breathing system was first described by Voss in 1985 [1], although it has been used in South Africa and Australia since the 1970s. It is an unusual anaesthetic breathing system in that similar fresh gas flows can be used for both spontaneous and mechanical ventilation.

The purpose of this study was to determine the fresh gas flow requirements of this breathing system necessary to avoid rebreathing during spontaneous ventilation.

Evaluation of the breathing system was undertaken in two groups of subjects. The first group contained 10 trained volunteers. The second groups contained 10 anaesthetized patients undergoing elective surgery. In both groups continuous recordings were made of minute ventilation (V_E), end-expired (E'_{CO_2}) and inspired carbon dioxide concentrations throughout the study.

The volunteer group were allowed to settle into a regular breathing pattern at high fresh gas flow rate (FGF). Subsequently the FGF into the breathing system was reduced by increments of 10 ml kg^{-1} min^{-1} at 15-min intervals.

In the anaesthetized patient group all patients received benzodiazepine premedication. Anaesthesia was induced with thiopentone 5 mg $^{-1}$ followed by suxamethonium 1 mg kg^{-1}. Topical lignocaine 3 mg kg^{-1} was applied to the larynx and nasotracheal intubation was performed. Anaesthesia was maintained with nitrous oxide in oxygen and 1.0% halothane. Following a period of stabilization (V_E, E'_{CO_2} stable) at high FGF the breathing system was studied at fresh gas flows of 100, 70 and 50 ml kg^{-1} min^{-1}. Rebreathing was said to occur when the criteria suggested by Kain and Nunn [2] were exceeded.

One volunteer showed evidence of rebreathing at FGF 90 ml kg^{-1} min^{-1} (FGF : V_E ratio 0.92). Four volunteers demonstrated rebreathing at FGF 80 ml kg^{-1} min^{-1} (FGF : V_E ratios 0.8–0.93) and five volunteers demonstrated rebreathing at FGF 70 ml kg^{-1} min^{-1} (FGF : V_E ratios 0.78–1.0).

One anaesthetized patient showed evidence of rebreathing at FGF 100 ml kg^{-1} min^{-1} (FGF : V_E ratio 0.7). Five patients demonstrated rebreathing at FGF 70 ml kg^{-1} min^{-1} (FGF : V_E ratios 0.53–0.81) and four patients demonstrated rebreathing at FGF 50 ml kg^{-1} min^{-1} (FGF : V_E ratios 0.56–0 72).

The fresh gas flow requirements of this breathing system did not exceed minute ventilation in any subject in either group. The fresh gas flow requirements of the Enclosed Magill anaesthetic breathing system are therefore similar to the requirements of the other Mapleson A circuits [3]. We suggest that, in order to avoid rebreathing, a fresh gas flow equal to minute ventilation should be used.

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OXYGEN SATURATION IN THE RECOVERY ROOM

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We have measured oxygen saturations in patients arriving in our recovery room after surgery, in an attempt to identify factors associated with hypoxaemia and to assess the clinical acumen of anaesthetists and nurses in detecting hypoxaemia.

Three hundred patients were studied following general, genito-urinary or E.N.T. surgery. Immediately after transfer to the recovery room, and while the patients breathed room air, an Ohmeda Biox 3700 pulse oximeter was applied to the finger [1]. The anaesthetist and the receiving nurse were asked if the patient was well oxygenated or cyanosed. They were unable to see the oximeter reading. The level of consciousness of each patient was also assessed on a five-point scale. A saturation of less than 90% was defined as hypoxaemia [2].

Of the 300 patients, 154 were male. The mean age was 49 yr (SD 19.8). Eighty-seven patients (29%) were hypoxaemic on arrival in the recovery room. There were no significant differences between the hypoxaemic and non-hypoxaemic patients with respect to sex, level of consciousness and grade of anaesthetist. Differences between these groups are shown in table XIX.

TABLE XIX. *Details of patients studied.* **$P < 0.001$ (*Mann–Whitney*), $r = -0.25$, $P < 0.001$ (*Spearman's*); §§ $P < 0.001$ (*Chi-square*); †† $P < 0.001$ (*t test*), $r = -0.29$, $P < 0.001$ (*Spearman's*)

	Hypoxaemic	Non-hypoxaemic
Mean (SD) age (yr)	56.2 (16.4)	46.7 (20.4)††
Major abdominal operations (%)	40	4§§
Median duration of operation (min)	57.5 (30/90)	35.0 (25/55)**
IPPV (%)	77	36§§

Twenty-seven percent of anaesthetists and 33% of nurses were incorrect in their assessment of the oxygenation of patients arriving in the recovery room. On assessing the hypoxaemic patients, 63% of anaesthetists and 44% of nurses described the patients as well oxygenated. This difference was significant ($P < 0.05$, Chi-square).

Hypoxaemia in our recovery room occurred in 29% of patients. Anaesthetists and nurses had difficulty in assessing oxygenation, especially in patients who were hypoxaemic. Some factors associated with hypoxaemia were identified.

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A MANUALLY-CONTROLLED INFUSION SCHEME FOR PROPOFOL

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An ideal infusion scheme for an i.v. anaesthetic agent produces the required blood concentration of the agent quickly, and maintains it constantly thereafter. Many different approaches have been made to achieve this with propofol, most using a single loading dose and various infusion rates thereafter. High initial blood concentrations have been a consistent feature of these studies.

Using a computer-controlled infusion system, based on a three-compartment model, a desired blood propofol concentration was quickly and consistently achieved without an initial overshoot [1]. We have modified this infusion profile to a scheme consisting of a single loading dose and three subsequent infusion rates, and assessed the resulting blood concentrations of propofol. The predicted blood propofol concentration was 3.0 $\mu g\ ml^{-1}$.

Ten healthy patients (51–87 kg), aged between 25 and 64 yr, having body surface surgery were studied for up to 90 min. Premedication was with temazepam 20 or 30 mg by mouth 1–2 h before operation.

Propofol was administered as follows: loading dose = 1 mg kg^{-1}; infusion rates = 10 mg $kg^{-1}\ h^{-1}$ for 10 min, 8 mg $kg^{-1}\ h^{-1}$ for 10 min, 6 mg $kg^{-1}\ h^{-1}$, thereafter.

The patients also received fentanyl 3 $\mu g\ kg^{-1}$, vecuronium 0.1 mg kg^{-1} and 67% nitrous oxide in oxygen. Gases were delivered by a Penlon Nuffield ventilator and a Bain system, and the end-tidal carbon dioxide concentration kept between 4.8 and 5.3 kPa. Venous blood samples for propofol estimation were taken from the antecubital fossa of the arm opposite to that of the administration. The samples were stored at 4 °C until analysed by an HPLC/fluorescence method.

The mean blood concentration of propofol during the whole study was 3.67 $\mu g\ ml^{-1}$. Concentrations at various times during the infusion are summarized in table XX. The initial arterial pressure values (mean 139/84 mm Hg) and heart rates (mean 80 beat min^{-1}) decreased gradually to their lowest values at 20 min (97/92 and 63, respectively). Average duration of infusion was 70 min, and the mean time to awakening following cessation of the infusion was 15.2 min (SD 8.6).

This manual infusion scheme has produced steady whole blood concentrations of propofol, without excessively high initial concentrations.

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PUPILLARY CHANGES AFTER CODEINE BY MOUTH

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Pupillary constriction after opioid drugs is related directly to plasma drug concentration after i.v. administration [1]. After administration of methadone by mouth the reduction in pupil size followed the same time course as the plasma drug concentration, but was not related directly to it [2]. We have measured pupil diameter and plasma codeine concentrations after the administration of codeine 60 mg by mouth.

After ethics committee approval and informed consent, 16 healthy voluntees aged between 18 and 24 yr were studied. After a 4-h fast codeine 60 mg or placebo was given by mouth with 50 ml of water in a double-blind, randomized manner. The studies were separated by 2 weeks. Pupil diameters and blood samples were measured at 0, 15, 30, 45, 60, 75, 90, 120 and 270 min after administration of the drug.

Pupil measurements were made using a pupillometer with standard lighting [3]. Each pupil measurement consisted of the mean of three values. Plasma codeine concentrations were measured using high performance liquid chromatography with fluorescence detection. Statistical analysis was by Student's *t* test.

There were significant differences in pupil diameter between the placebo and codeine groups from 45 to 120 min (fig. 7). Although there was no correlation between the plasma codeine concentration and pupil size, there was a significant relationship ($P < 0.01$) between the reduction in pupil size and the area under the plasma concentration–time curve at 60 min.

TABLE XX. *Whole-blood propofol concentration ($\mu g\ ml^{-1}$) at various times during infusion scheme*

	Time during infusion (min)									
	2	5	10	15	20	30	40	50	60	80
Concn										
Mean	3.62	3.24	3.98	3.62	3.76	3.39	3.57	3.86	4.07	3.79
SD	1.15	0.83	0.87	0.74	0.57	0.55	0.50	0.57	0.85	1.04

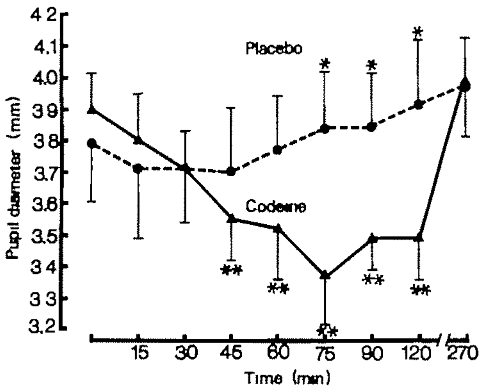

FIG. 7. Changes in pupil diameter in subjects receiving codeine 60 mg by mouth or placebo.

Codeine produced a reduction in pupil size that was proportional to the amount of drug absorbed.

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COMPARISON OF SINGLE TWITCH AND TRAIN-OF-FOUR MODES OF STIMULATION FOR MEASUREMENT OF NON-DEPOLARIZING NEUROMUSCULAR BLOCK

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Neuromuscular blockade is usually monitored using either single twitch (ST) or train-of-four (TOF) stimulation. Both modes of monitoring have been used to determine potency, speed of onset, duration of action, recovery and adequate antagonism of neuromuscular blockade. It is generally assumed that the first response (T1) in the TOF stimulation provides the same information as the ST stimulation. However, a recent study has shown that this may not be so [1].

In the present study the speed of onset of neuromuscular block and time to recovery of 25% twitch height with atracurium and vecuronium were compared using ST (at 0.1 Hz) and TOF (at 2 Hz every 10 s) modes of stimulation. Neuromuscular block was monitored by stimulation of the ulnar nerve and recording the force of contraction of adductor pollicis.

Eighty healthy adult patients scheduled for elective surgery gave informed consent to participate in the study which had been approved by the local Ethical Committee. Following premedication with diazepam by mouth, anaesthesia was induced with thiopentone and maintained with nitrous oxide in oxygen and incremental doses of fentanyl. Patients were randomly allocated to be stimulated supramaximally at rates of 0.1 Hz or 2 Hz in a TOF sequence every 10 s and to receive atracurium 225 or 450 μg kg^{-1} or vecuronium 40 or 80 μg kg^{-1}. Time to onset of maximal block and duration to recovery of 25% twitch height of ST or T1 of TOF was measured.

The results (table XXI) were subjected to analysis of variance and *t* tests.

TOF stimulation resulted in a significantly more rapid onset of action at both doses of atracurium. However, the time to 25% recovery of twitch height was significantly prolonged only in those receiving 225 μg kg^{-1}. Neither the onset nor recovery of vecuronium was significantly altered by the mode of stimulation at either dose.

TABLE XXI. *Onset and duration of action of atracurium and vecuronium with ST and TOF stimulation (mean ± SD).* *P < *0.05;* ***P < *0.005*

	Onset (s)		Duration (min)	
	ST	TOF	ST	TOF
Atracurium				
225 μg kg^{-1}	468±112***	191±45	18.6±7.8*	26.7±7.6
450 μg kg^{-1}	203±119*	104±30	43.2±12.6	43.0±8.6
Vecuronium				
40 μg kg^{-1}	299±121	259±64	16.7±4.1	14.3±2.8
80 μg kg^{-1}	176±43	131±57	33.1±7.9	28.3±7.8

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COMPRESSION OF DATA FROM PULSE OXIMETRY BY DELTA MODULATION

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Only some of the existing pulse oximeters can store data, then only for a maximum of 8 h and with inevitable loss of detail and flexibility because of time-averaging and the limitations of the graphical representations of the oximeters. We have written and tested a program for a BBC microcomputer that captures pulse rate and oxyhaemoglobin saturation as frequently as any pulse oximeter can provide the data, stores the values economically on disc over long periods, and returns them at the original time resolution. These can then be processed and displayed in a variety of ways.

Most pulse oximeters have an analogue output signal of pulse rate and saturation that can be displayed on a chart recorder or other device. In our system this analogue output is sampled in real time by the standard A–D converter of the BBC microcomputer and is averaged over any chosen period, or a default period of 1 s. The program works as an event marker for both pulse rate and saturation. The initial values are stored in a program buffer and, when either of the values changes, the new pair of values and the time of the change are recorded. The change, in pulse or saturation, must be greater than a threshold value (designated by the user) to be recognized as a change. The program buffer of stored data is emptied to disk each hour, or earlier if 400 events have been recorded.

The data can be retrieved and displayed as:

(1) one or both variables plotted on a time scale of between 1 min and 24 h;

(2) pulse rate plotted against oxyhaemoglobin saturation;

(3) histograms of the percentage of time spent at each saturation, over a chosen period of between 1 min and the total duration of the recording.

We have tested the system on ourselves overnight and during controlled hypoxia induced by rebreathing, and in overnight studies on medical and surgical in-patients. Direct on-line chart-recordings and retrospective computed plots of the stored data compare well. We have been unable to identify any changes in the real-time recordings which were not accurately identified and timed by our program, nor has the program detected any changes when the values were stable.

MEASUREMENT OF THE FORCE REQUIRED TO HOLD OPEN THE MOUTH

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The jaw muscles are important to the anaesthetist because they must be manipulated in order to intubate the trachea. There is anecdotal evidence that the administration of suxamethonium can sometimes be followed by difficulty in opening the mouth. There are also case reports of "masseter spasm", prolonged rigidity and of regional muscle contracture following administration of suxamethonium [1–3].

To investigate this phenomenon, it would be useful to measure the force required to hold open the mouth in the anaesthetized patient. To this end we have developed a device to be placed between the front teeth which will estimate the force required to hold open the mouth a preset width, which we have arbitrarily chosen to be 3 cm. The device consists of a calliper modified to incorporate strain gauges in the arms and plastic coated atraumatic platforms for insertion between the front teeth so that the mouth may be opened in the midline. A spirit level allows measurements to be made in the plane perpendicular to the front teeth and a spacer must be inserted to hold the device open by 3 cm so that it is merely supported while the measurement is being made. The signal from the strain gauges is amplified and recorded on paper. Calibration before use is achieved by lifting 350-g and 700-g weights the vertical distance of 3 cm in a specially designed frame.

TABLE XXII. *Validation of the device*

Weight (g)	Reading (SD)	95 % Confidence intervals	Deviation (%)
500	496 (7)	482–510	3.6
1000	1002 (12 3)	977–1026	2.6
1500	1502 (24.8)	1452–1552	3.5
2000	2000 (41)	1918–2082	4.1
2500	2495 (36.9)	2421–2568	2.8
3000	3010 (45)	2920–3100	3.3

Validation of the device was carried out in the following manner: known weights in 500-g increments up to 3 kg were lifted in the frame. Ten measurements were made with each weight and the mean and standard deviation of the readings obtained were calculated. The device was linear up to 3 kg, the mean of the 10 readings at this weight being within 1.5 % of the true value. As an estimate of the accuracy of the device, 95 % confidence intervals for the measurements are listed, together with their percentage deviation from the true weight, in table XXII.

The reproducibility of the measurement was observed in a skull model incorporating springs of different strengths to hold the jaws together. The effect on the measurements of extending the head was also investigated. Coefficients of variation with two sets of springs, making 10 measurements with the skull in each of three positions of head extension (0, 10 and 20°) were 1.9 % with springs requiring a force of 650 g weight to hold the jaws 3 cm apart, and 2.5 % with springs requiring a 1.5-kg force.

There was no drift in the calibration over 24 h.

Maximum deviation from the actual weight measured was less than 5 % of the weight, so clinical differences would have to be 5 % or more to be detectable.

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STABILITY OF ATRACURIUM IN DILUTE SOLUTIONS

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Infusions of atracurium are increasingly used to facilitate mechanical ventilation in the Intensive Care Unit. In paediatric practice a dilution of 1 in 10 is commonly used. Concern has been expressed that degradation of atracurium in the syringe pump may contribute towards the apparent increase in infusion requirement observed over a period of many hours [1]. Previously published data are confined to a dilution of 1 in 20 in physiological saline or lactated Ringer's solution [2].

TABLE XXIII. *Percent decrease in atracurium concentration*

Time (h)	1 in 2 dilution D	S	W	H	1 in 10 dilution D	S	W	H
6	2.0	2.3	5.3	7.7	2.0	2.2	6.0	6.3
24	2.3	5.0	8.3	12.7	2.7	3.0	9.7	17.7
48	4.5	7.3	10.0	19.7	4.3	9.3	25.0	39.0

Atracurium besylate taken from the ampoule was diluted 1 in 2 and 1 in 10 with 5% dextrose (D), 0.9% saline (S), sterile water (W), or Hartmann's solution (H) to a volume of 5 ml in plastic syringes. Each dilution was performed in triplicate. The syringes were maintained at 30 °C and 100-μl samples were removed immediately and at 6, 24 and 48 h, acidified and immediately cooled to −20 °C. The concentrations of atracurium and laudanosine in each sample were estimated using high performance liquid chromatography using the method described by Simmonds [3].

The mean percentage decrease in atracurium concentration with time is shown in table XXIII. The stability of atracurium in the various diluents was as follows: D > S > W > H and, in general, 1 in 2 > 1 in 10 dilution. Very little degradation of atracurium took place in 48 h when diluted 1 in 2 or 1 in 10 with 5% dextrose. If dilution of atracurium is necessary, the most suitable diluent would therefore appear to be 5% dextrose.

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MASSETER MYOTONIA WITH SUXAMETHONIUM

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Recently an increase in jaw tone in normal children was reported following i.v. suxamethonium [1], but no similar observation appears in the literature for adults. Masseteric myotonia (spasm) can be a presenting sign of malignant hyperthermia [2, 3]. This study was designed to assess the changes in jaw tone following an intubating dose of suxamethonium, using a tonometer specially devised and constructed in our department.

The two arms of the tonometer were positioned between the teeth, and tone generated was measured using a strain gauge, and recorded on a flat bed recorder. Jaw separation was maintained using an appropriate preload (mean 900 g weight). Electrically evoked twitch of the small muscles of the hand using supramaximal stimulation at a frequency of 1 Hz was monitored.

Twenty fit adults presenting for surgery were studied. Anaesthesia was induced following preoxygenation with a sleep dose of thiopentone, and maintained using an oxygen–nitrous oxide mixture. Suxamethonium 1.0 mg kg^{-1} diluted to 5 ml with saline, was injected slowly (mean 9.5 s). Continuous recordings of jaw tone, muscle twitch and ECG were made, until all tone changes had returned to baseline. Laryngoscopy and cord paralysis were then assessed. Parametric results were analysed using Student's paired *t* test.

Eighty-five percent of patients showed increases in jaw tone, the onset time being 10.4 ± 6.9 s (mean ± SD), with a duration of 29.7 ± 9.2 s. This contrasted significantly ($P < 0.025$) with the 90% of patients who fasciculated, the onset time being later (14 0 ± 5.9 s) with a duration of 19.1 ± 8.4 s.

A wide variation was found in maximum tone produced, 693 ± 603.5 g peaking at 21.8 ± 10.8 s. However, four patients (20%) generated tone well in excess of 100 g, the maximum being 2425 g. Offset of tone occurred at 40.1 ± 13.1 s, which was significantly later than fasciculation offset time 33.0 ± 8.6 s ($P < 0.02$). Eight out of 15 patients were still generating considerable force (maximum 1000 g) 10 s after the end of fasciculations. An inverse linear relationship was found between maximum tone generated and age ($r = 0.43$, *P* < 0 05). Full visualization of fully paralysed cords was noted in all patients.

From the results of this study, it would seem that fasciculations provide an inadequate index for optimum time of intubation. It follows that the clinical diagnosis and incidence of masseter myotonia may be very subjective, and hence its impact in relation to making an early provisional diagnosis of malignant hyperthermima is open to doubt.

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COMPARISON OF PROPOFOL AND METHOHEXITONE AS ANAESTHETIC AGENTS FOR ELECTROCONVULSIVE THERAPY (ECT)

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EVALUATION OF THE TRIFLO II INCENTIVE DEEP BREATHING EXERCISER AFTER CHOLECYSTECTOMY

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Bateman [1] proved the benefits of chest physiotherapy in clearing the lungs of excessive secretions—a common problem after upper abdominal surgery—which may lead to atelectasis and infection. Chest physiotherapy for postoperative patients is expensive and time consuming, adding considerably to the workload of the physiotherapy department.

Sixty patients were allocated at random to a study; in 30 of

TABLE XXIV. *FEV_1 (litre (mean (SD)) in the two groups.* *$P < 0.05$; ***$P < 0.001$

	Control	Triflo II
Pre-op.	1.95 (0.6)	1.96 (0.7)
Day 2	1.07 (0.4)**	1.32 (0.4)**
Day 5	1.61 (0.5)	2.04 (0.7)

them the benefits of self-administered physiotherapy using the Triflo II and breathing exercises were evaluated after cholecystectomy, whilst the remaining patients acted as controls. All patients were free of respiratory and cardiac disease and conformed to ASA groups I and II. Ethics permission and the informed verbal consent of the patients were received. Ventilatory function tests (ventilatory frequency, FEV_1 and vital capacity) were recorded before operation and on the 2nd and 5th days after operation.

The results (table XXIV) show that ventilatory function tests were significantly decreased ($P < 0.01$) in both groups on the 2nd day after operation.

FVC had virtually returned to normal on the 5th day after operation in both groups, with the ventilatory frequency and FEV_1 remaining significantly decreased in the control group.

In conclusion, use of the Triflo II and breathing exercises are reliable in maintaining ventilatory function in healthy patients after cholecystectomy.

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CORRESPONDENCE

AVOIDING ACCIDENTAL DURAL PUNCTURES

Sir,—The incidence of accidental dural puncture during extradural catheterization depends largely on the expertise of the operator, on the technique used, and on the suitability of the patient. A dural tap with an extradural needle can cause much distress to the patient and should be avoided as far as possible. A simple modification of a standard technique is described here which can contribute to reducing the incidence of accidental dural puncture. This technique is particularly suitable for those patients with very soft or very hard ligaments, in whom an accidental dural puncture is most likely.

In this technique it is essential to utilize a glass syringe with free movement between the barrel and the plunger, but with no leak past the plunger. These points must be confirmed before commencing. The extradural needle is introduced up to the ligamentum flavum using standard technique and the syringe, loaded with saline, is firmly attached. Using conventional technique, the syringe is advanced, applying constant pressure at the plunger. In this modified technique the assembly of syringe and needle is advanced *by pushing the plunger of the syringe only*. The barrel of the syringe is not actively advanced but only supported by the free hand. While the needle tip is advancing through the ligamentum flavum it is occluded, and the whole assembly will advance as one. Once the tip of the needle is past the ligament, egress of saline is again possible and the plunger will collapse into the syringe, leaving the needle and attached barrel immobile. The sudden injection of saline probably contributes to the safety of this technique by pushing the dura away from the tip of the needle. The patient feels a cold sensation in the back, and should be forewarned about this. The end-point is sudden and definite, even in difficult patients. It is possible for the needle tip to be left only partly through the ligamentum flavum, although this can be overcome by conventional techniques. This problem occurs surprisingly rarely.

When the patient has very hard ligaments, it is advisable to pinch the needle gently between thumb and forefinger of the free hand. This reduces the tendency of a sudden give which would carry the needle through the dura.

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MODIFIED I.V. CANNULA USED FOR NERVE STIMULATION

Sir,—We would like to report the use of a modified cannula used for nerve stimulation. When brachial plexus blocks (axillary block), or lumbar plexus blocks ("3-in-1-block") [1] are performed, electric stimulation of the nerve is often used as a reliable and convenient method of identification. Specially constructed needles, of which only the point is conductive, are used. This gives a more reliable identification and fewer complications than when using a non-insulated hypodermic needle [2,3]. Such needles are expensive. Instead of using an original insulated stimulation needle, we have used a modified i.v. cannula.

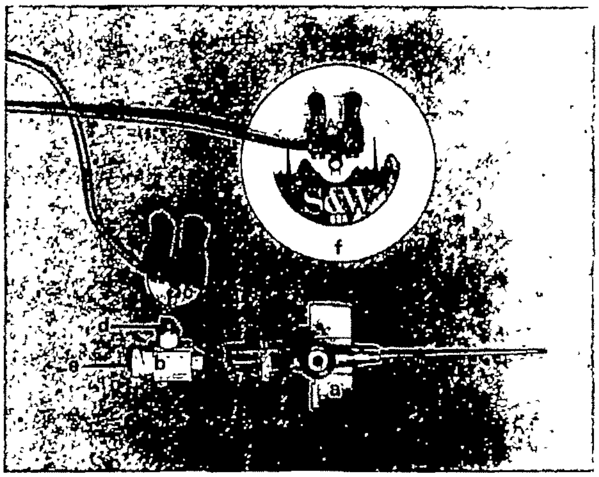

Fig. 1. The modified i.v. cannula. a = Cannula; b = adaptor; c = lead from nerve stimulator; d = male button; e = connecting pipe; f = ECG electrode as ground lead.

For this modification we have used (fig. 1) an i.v. cannula (Venflon) G.1.2 (a) on which an "Arrow-Johans ECG adapter" (b) has been fitted. The adaptor has a stainless steel male button (d). A lead from a nerve stimulator (c) is connected to the male button. An ordinary ECG electrode is used as the ground lead (f). Sodium chloride 0.9%, which is used as conductive solution between the ECG adaptor and the metallic cannula in the Venflon, is injected through the connecting pipe (e). The cannula is now ready for use. The system is aseptic and the local anaesthetic may be injected directly through the adaptor as soon as the nerve or the nerve plexus has been identified.

Furthermore, it is possible to leave the sheath from the cannula *in situ* for further anaesthetic injections.

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FAILURE TO DEMONSTRATE *IN VITRO* METABOLISM OF MORPHINE IN WHOLE BLOOD AND PLASMA

Sir,—A drug administered i.v. may be subject to rapid transformation by enzymes present in plasma or whole blood or by non-enzymatic processes. This is often a desirable feature of drugs used in anaesthetic practice. Clinically important drugs transformed enzymically or non-enzymically in blood include suxamethonium [1], cocaine [2], procaine [3], propanidid [4] and atracurium. A review of the disposition of opioids [5] highlighted their widespread biotransformation in human tissue.

To our knowledge no substantial information has been produced on the *in vitro* metabolism of morphine in whole blood or plasma, bearing in mind that most analyses for morphine and its metabolites are performed almost exclusively on plasma or whole blood.

The purpose of this study was to investigate whether morphine undergoes *in vitro* biotransformation in oxygenated whole blood or plasma at 37 °C. If this does occur, serious difficulties may be encountered in interpreting morphine concentrations in blood and plasma stored at room temperature before their analysis.

One hundred millilitre of whole blood was withdrawn from a vein of a single volunteer; 50 ml was centrifuged at 3000 rev min^{-1} to harvest the plasma fraction. Whole blood and plasma specimens were then incubated in lithium–heparin tubes at 37 °C and morphine was added to give a concentration of 1 μg ml^{-1}. The specimens were kept oxygenated by gently bubbling air through the samples and were mixed to achieve a homogeneous morphine concentration. Plasma samples obtained from both whole blood and plasma specimens were analysed at the following times: immediately after mixing and then at 2, 4, 6, 12, 24 and 48 h by a modification of a specific high performance liquid chromatographic procedure [6].

The results are summarized in table I. The failure to detect metabolites indicates that, under the conditions used, no transformation or breakdown of morphine occurred at 37 °C over the 48-h study period. Mean recovery of morphine from whole blood was 90%; that from plasma was 99% ($P < 0.1$).

Morphine is primarily metabolized *in vivo* by glucuronidation catalysed by microsomal UDP-glucuronyl transferse. In man, the major part of a dose of morphine is excreted in the urine as morphine glucuronides. Other metabolic pathways include the formation of normorphine and morphine ethereal sulphate . Nonetheless, the metabolic fate of morphine in man is not entirely elucidated and 10–20% of a given dose still remains to be accounted for [7], possibly by retention in the centrifuged blood cells. This *in vitro* investigation showed that, under the conditions used, morphine is not metabolized in whole blood or plasma. A further study is planned to establish whether or not morphine enters the blood cells and causes the discrepancy between whole blood and plasma assays.

TABLE I. *Peak heights of morphine in plasma and whole blood. No metabolites were detected*

Time (h)	Whole blood (mm)	Plasma (mm)
0	161	199
2	171	224
4	150	136
6	150	154
12	126	141
24	153	173
48	139	131

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OPIOID PREMEDICATION AND BILIARY COLIC (THE FIRST INDICATION OF BILIARY PATHOLOGY)

Sir,—We would like to report a case of a 32-year-old woman scheduled to undergo diagnostic laparoscopy because of chronic pelvic pain. Before operation, the patient was generally well and, in particular, had no signs or symptoms of gastrointestinal disease. Premedication with papaveretum 15 mg and prochlorperazine 12.5 mg was administered by i.m. injection 1 h before surgery. Approximately 30 min later the patient developed severe colicky upper abdominal pain associated with retching. This resolved spontaneously after a further 30 min. Opioid-induced biliary colic was suspected and the laparoscopy was postponed. An ultrasound examination of the gall bladder revealed a distended gall bladder which appeared to contain more than 100 small stones. Before the premedication, there had never been any symptoms of biliary disease. A surgical opinion was obtained and arrangements were made for cholecystectomy. At operation some 6 weeks later, the diagnosis of multiple gall stones was confirmed and cholecystectomy carried out. Operative cholangiography was normal and an explanation for the chronic pelvic pain was provided by the finding of bilateral hydrosalpinges.

On reviewing the limited literature concerned with opioid-induced biliary colic, it would appear that case reports relating to this problem all concern patients who have had or are about to have biliary surgery [1–3]. This raises the possibility that opioid-induced colic is not a pharmacological response, but rather biliary tract pathology is a pre-requisite for it to occur. Biliary pressure studies have demonstrated biliary hypertension and spasm of the sphincter of Oddi as a common consequence of opioid administration. The results of these studies may be misleading as, by necessity, the measurements are made during the course of cholecystectomy (i.e. there is proven biliary disease) and, furthermore, pressures are measured by cannulation of the cystic duct (after the gall bladder has been removed), which is not a particularly physiological situation [4–6]. This view point is endorsed by canine studies which revealed that biliary pressures did *not* change in healthy dogs following administration of opioids unless the gall bladder had previously been removed [7]. This raises the possibility that the gall bladder is functioning as a pressure valve and limiting opioid-induced effects. On the basis of these observations, we would suggest that it is perhaps only those patients with an absent or non-functioning gall bladder who are at risk of opioid-induced colic. It may be, therefore, prudent to investigate the biliary tract in such patients rather than to dismiss the problem as a pharmacological response.

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SUXAMETHONIUM AND INTRAOCULAR PRESSURE

Sir,—After reading the paper on the changes in intraocular pressure changes during induction and intubation associated with the administration of thiopentone or propofol [1], I felt that an important result of the study was rather ignored.

The results in table II clearly show that the combination of induction and suxamethonium did not cause a significant increase in intraocular pressure in any group when compared with baseline values. However, the authors preferred to use the post-induction values of intraocular pressure, and to state—in the summary—that there was a significant increase in intraocular pressure following suxamethonium. Yet the authors used baseline intraocular pressure as their reference point to comment on the lack of a significant increase in intraocular pressure with the combination of a second dose of propofol and intubation. (The use of the "post second dose induction value" of intraocular pressure, a reference point similar to that used when stating the significant increase in intraocular pressure with suxamethonium, would of course have given the result of a significant increase in intraocular pressure.)

Surely, the authors should be consistent (with reference points) when using statistics to conclude the possible beneficial effect of certain therapeutic measures. If it is "true" that a second dose of propofol protected against the increase in intraocular pressure secondary to intubation, then it is also "true" that suxamethonium did not cause an increase in intraocular pressure.

When considering the problem of how to maintain a stable intraocular pressure during induction and intubation, surely both these facts are equally important.

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Sir,—Thank you for giving me the opportunity to reply to Dr Edmondson's letter. While Dr Edmondson is correct in pointing out that we used the post-induction value intraocular pressure (IOP) for comparing the increase in IOP after suxamethonium administration, it was clearly stated in the text that, even after suxamethonium administration, the IOP was never significantly greater than the baseline value. The use of post-induction values after suxamethonium was used purely to show the increase that occurs in IOP following suxamethonium administration. Further, it was stated in the results section of our paper, that intubation did increase the IOP in all groups, although the IOP in the supplementary-dose propofol group did not exceed the baseline value.

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ANTI-NEOPLASTIC SYNERGISM OF NITROUS OXIDE AND METHOTREXATE

Sir,—The review article by Nunn [1] mentioned a suggestion by Ueland and co-workers [2] that the side effects associated with methotrexate could be increased, and the efficacy of leucovorin rescue be decreased, by anaesthetic regimens in which nitrous oxide is used. They further suggested that, until these possibilities have been rejected "...nitrous oxide should be used with caution in patients receiving methotrexate".

Nunn went on to suggest that this theoretical problem has not been investigated. However, there is some work which indicates that, far from causing problems in association with methotrexate, nitrous oxide may well have a positive synergistic action. For instance, it has been shown *in vitro* that a combination of nitrous oxide and methotrexate was more effective in depleting functional folate than either agent alone, indicating the possibility that these agents might act synergistically as anti-neoplastic agents *in vivo* [3]. Furthermore, whilst the rescue effect of 5-methyltetrahydrofolate is diminished following exposure to nitrous oxide, this was not the case with 5-formyltetrahydrofolate (folinic acid) [4].

Such a finding is not unexpected, since both nitrous oxide [1,3,5] and methotrexate [3,4,6] appear to disrupt steps in folate metabolism only before the formation of folinic acid. It is, therefore, not surprising that, according to Ueland and colleagues [2] the "rescue therapy seems to work in children exposed to nitrous oxide". Indeed, this rescue effect of adequate doses of folinic acid has been shown quite clearly to prevent megaloblastic bone-marrow changes in most human subjects following extended analgesic and anaesthetic exposures to nitrous oxide [1,7]. It would appear, therefore, that the presence of nitrous oxide is unlikely to have an effect on the rescue effect of leucovorin, whilst possibly having a positive anti-tumour action through its synergism with methotrexate [3].

Therefore, far from decrying the use of nitrous oxide in conditions sensitive to folic acid antagonists (such as methotrexate), the possibility of using these agents in combination with the gas should be further investigated. Such investigations could lead to better disease control or reductions in the doses of methotrexate used. Apart from its synergistic anti-neoplastic effect in this context, nitrous oxide would have the further advantage of being an excellent analgesic [8].

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CATHETER EROSION OF VESSEL WALLS

Sir,—Recently, I observed an interesting series of events in a cachectic elderly male patient suffering from chronic pancreatitis. He had been admitted to an Intensive Therapy Unit on account of pulmonary oedema, and for parenteral nutrition to improve his condition in anticipation of further surgery. A 16-gauge Teflon catheter was sited in the left internal jugular vein (after blockage of a catheter in the right side). Approximately 48 h later, the patient complained of chest pain; this was mainly central, but with some associated discomfort in the left shoulder. Clinical examination was normal, as were an ECG, chest radiograph and arterial blood-gas tensions. Dextrose 50% was being infused through the central venous catheter, from which blood could be freely obtained by gravitational reflux.

Pulmonary embolism or myocardial ischaemia was suspected. Sublingual glyceryl trinitrate was given, and the patient's pain appeared less. He was instructed to bite, and retain orally, a capsule of nifedipine, but this provided no further benefit. Morphine was then given slowly i.v. until he was comfortable (total 17 mg). He slept for the remainder of the night, during which time Intralipid as well as dextrose was given through the internal jugular catheter.

A chest radiograph obtained the following morning, approximately 12 h after the onset of pain, showed a large left-sided pleural effusion (fig. 1.). This was tapped and 200 ml of milky fluid obtained. Although blood could still be aspirated from the central venous catheter, it was removed. A chest drain was inserted, from which over 900 ml of milky fluid drained during the following 24 h. There were no further complications.

This report demonstrates that the ability to aspirate blood from a central venous catheter is not an absolute guarantee that a subsequent injection or infusion will be i.v. Presumably, the tip of the catheter eroded the vein, so that the catheter opening lay partly within the vein and partly within the pleural space,

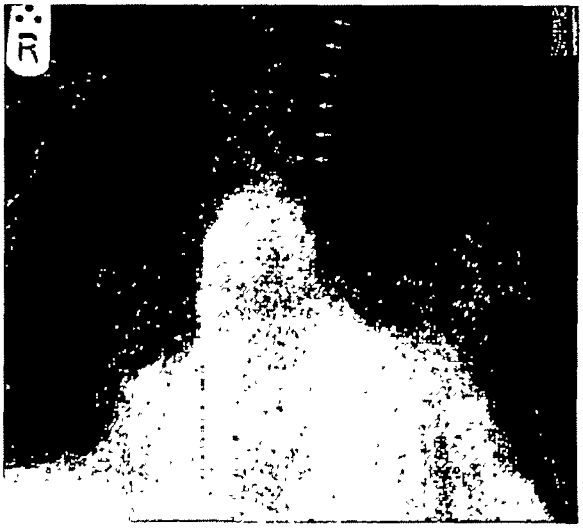

FIG. 1. Antero-posterior chest radiograph showing the large left-sided pleural effusion. The position of the internal jugular vein catheter is arrowed. The opposing pair of arrows indicates the tip of the catheter.

so that infused fluid could flow preferentially to the negative pressure of the pleural space, whilst blood could still be aspirated.

Others have been alerted to this problem after finding inappropriately low central venous pressures [1]. Twelve years ago Carvell and Pearce [2] reported their own experience of bilateral hydrothoraces as a result of catheter erosion, and reviewed the relevant literature. More recently, Sheep and Guiney [3] have reported three patients who suffered complications (including fatal cardiac tamponade) from extravasation of fluid through catheters inserted via the left internal jugular vein. They point out that the circuitous route for venous return from the left side is likely to predispose to erosion of vessel walls if stiff catheters are used, and that such catheters were designed for the right-sided approach. The catheter used in the patient I observed fits this description and, in retrospect, a more flexible catheter should have been inserted.

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BOOK REVIEWS

Common Problems in Obstetric Anesthesia. Edited by S. Datta and G. W. Ostheimer. Published by Year Book Medical Publishers, Inc. Chicago and London. Pp. 496; indexed; illustrated. Price £38.50.

This book, edited by Drs Datta and Ostheimer of the Brigham and Women's Hospital, Boston, has a total of 66 contributors. The preface states that this is not a typical textbook, but rather a selection of cases that suggest management techniques. This is indeed a novel approach and a number of the chapters make very good reading with sound advice on management of specific obstetric and anaesthetic problems. Many of the chapters are written almost as answers to examination questions and this format may appeal to the examination candidate.

The text consists of just under 500 pages with few diagrams, and this is not a book to be read cover-to-cover. There is much repetition in the text which, on occasions, is deliberate as the Editors have sought views on a particular problem from different centres within North America. Herein may lie its strength as, although the text is often dogmatic, it is apparent that opinions differ and alternative techniques may be used when one is faced with particular obstetric or anaesthetic problems. It is interesting to see the occasional Editor's note in the text when the Editor's view differs from that of the author.

Naturally, this book presents a North American view, particularly in regard to the utilization of spinal anaesthesia for operative delivery and the management of toxaemia of pregnancy. The availability of different drugs within North America and the United Kingdom influences the management of individual problems and the U.K. reader will find this a disadvantage. It was pleasing to see the emphasis on regional anaesthesia in obstetrics, and both spinal and extradural anaesthesia are well covered.

The chapters on Trial of Labour following Cesarian Section and Anesthesia for Cesarian Section are excellent reviews. Spinal headache and neurological complications following extradural anaesthesia are particularly well covered. It was disappointing, however, not to see disseminated sclerosis or other chronic neurological diseases mentioned in the chapter "Anesthesia for Parturients with Neurological Problems," but the author had simply been asked to describe the management of a patient with paraplegia. A failed intubation drill was not described, although failed intubation was repeatedly mentioned as causing maternal mortality.

The text is very well referenced by most authors, although some simply preferred to list a bibliography at the end of their chapter. This is indeed an up-to-date presentation, with many recent references so often missing from the medical text book. It is a practical book which deserves reference to by the obstetric anaesthetist and the trainee.

J. H. McClure

Decision Making in Anesthesiology. By L. L. Bready and R. B. Smith. Published by B. C. Decker Inc., Toronto and Philadelphia. Pp. 281; indexed; illustrated.

Most anaesthetic text books seem to be structured by defining general principles from which the reader has to work out the solutions to the particular problems that face him. In recent years decision theory has been used to analyse how we come to decide what to do in particular circumstances. Often a tree is constructed showing the various options available and the factors which will guide the selection of a particular path. This book presents this type of analysis for a large number of anaesthetic problems. Drs Bready and Smith with their colleagues from Texas have constructed 134 algorithms dealing with the choices of anaesthesia for situations varying from the choices of general or regional anaesthesia for healthy patients to the management of the neonate with necrotizing enterocolitis, the cigarette smoker, the diabetic patient and those with a phaeochromocytoma. Virtually all the examiners' favourite problems are present. the bleeding tonsil, the open eye injury, the child with epiglottitis, and surgery in the sitting position. The solutions to the problems are reasonable but, as might be expected, weighted towards standard North American practice. Each algorithm is accompanied by a page of notes which give further details, and explanations, of the choices made, together with a small selected reference list. Again, and somewhat sadly, these lists are heavily weighted by North American publications and a relative absence of European information.

Nevertheless, this is a stimulating approach which will provoke the reader into comparing his techniques with those advocated. A copy in a departmental library will be useful as a source of topics for discussion. For examiners and candidates the book should provide a source of alternative questions—and answers. The reader will have to become used to the North American spelling and the love of symbols. Fortunately, most are defined, and on the pages where they occur. Some are ugly: I do not like GETA for general endotracheal anaesthesia, but fear it may become as popular as intravenous access.

J. Norman

Renal Physiology: Principles, Structure and Function, Second Edition. By E. Koushanpour and W. Kriz. Published (1986) by Springer-Verlag. Pp. 390; indexed; illustrated. Price (approx.) £42.00.

This is a welcome second edition of a book that was very well received when it appeared first. It is based on a lecture course in renal physiology given by Professor Koushanpour at North Western University Medical School, although I cannot imagine that even North American medical students are expected to absorb this amount of information about the kidneys. It is an excellent work. It presents an integrated, quantitative analysis of renal function and the kidneys' important role in the homeostasis of body fluids.

This book is quite different from a conventional renal physiology text; it is not descriptive, but is based on systems analysis and mathematics. At the start of each chapter is a summary of the contents and then each topic is dealt with separately and thoroughly. The current state of understanding is explained and the authors make it clear where there are major gaps in our knowledge and where research is needed.

The use of systems analysis will be unfamiliar to most readers, but the authors' clear explanations and good line diagrams soon convince the sceptic that this is an interesting and worthwhile approach. It facilitates understanding of complex processes and enables the student to see how an alteration in one part of the system has major effects on later components. The other strength of this particular work is its ability to synthesize anatomical structure with functional integrity, particularly in the workings of the countercurrent exchange in the medulla.

The book is well supplied with electron micrographs, line drawings and figures, most of which are well presented; it is peppered with small chunks of mathematics, which are clear and essential for anyone attempting to understand the processes of tubular transport, for example. However, the authors' explanation of concepts is quite clear, so that less numerate but interested readers may skip the mathematics without great loss. Each chapter contains a list of up to date references and the volume is well indexed.

This is not a book for the faint-hearted because it is a systematic and more rigorous approach to renal physiology than is taught conventionally in British medical schools. I have found it an excellent reference work and I think it should find a place in any serious library where renal physiology is being regularly taught, researched or consulted in the interests of patient care.

C. P. Swainson

The Therapy of Pain, Second Edition. Edited by M. Swerdlow. Published by M.T.P. Press Ltd. Pp. 260; indexed; illustrated. Price £32.95.

The first edition of Mark Swedlow's "The Therapy of Pain" was published as a multi-author text in 1981. The second edition is of similar format, but has been considerably updated, rewritten in several sections and extended. The three rewritten chapters are those on neurophysiology, oncology and nerve block techniques and there are new chapters on assessment of the pain patient and on low-back pain. The title is slightly misleading, as the book confines itself to chronic and cancer pain, with no consideration of acute or postoperative pain.

The book consists of 260 text pages, with black and white illustrations where appropriate, collected into 11 chapters—each by a different author. The list of contributors is a veritable "Who's Who" in the chronic pain field, but their different styles have been skilfully adjusted so there is a pleasing uniformity throughout the book. Professor Cervero opens with an excellent review of basic neurophysiology but, some would say fortunately, stops short of detailed description of the multiplicity of endogenous opioids, peptides and potential transmitters. Nor, disappointingly, was there much discussion on the origin of frequently-seen neurogenic pains such as post-herpetic neuralgia, causalgia or sympathetic dystrophy. Professor Pilowsky's chapter on the rôle of the psychiatrist remains essentially unchanged except for a short section on the use of tricyclic antidepressants. Dr Sam Lipton's advice on the management of a pain relief service, based as it is on his vast experience, remains a most useful theoretical and practical guide. The Editor, Dr Mark Swerdlow, has added a section of his own on the assessment of pain patients and Dr Williams follows with a review of pharmacological treatment. Dr M. Mehta's chapter on non-invasive techniques is a useful review, but rather short on detail. The rôle of nerve block techniques is discussed in an excellent chapter by Dr Ed Charlton. Although details of practical block technique are not discussed, the priciples behind the use of local anaesthetic and chemical neuroablative procedures are very well argued and are of particular relevance to anaesthetists. The neurosurgeon's view is put by Professor Ted Hitchcock and in this section radiofrequency destruction of various areas is discussed, together with stimulation techniques. Three specialist chapters, on oncology in cancer pain by Dr E. Robinson, low back pain by Mr Porter and cancer pain by Dame Cecily Saunders conclude the text.

The subject of chronic pain is expanding so quickly at present that this type of book is of great value as a review of the various disciplines involved. Because each chapter is relatively short there is, of necessity, a lack of detail in many respects, but to a great extent this is compensated for by an extensive reference section of between 60 and 160 references per chapter. The majority of the text is clear, concise and well illustrated, although some of the photographic illustrations are not well done. The index is extensive and easy to use.

This second edition was a pleasure to read, has a great deal to offer every level from the undergraduate to the trainee and specialist in many fields, including anaesthesia. Dr Swerdlow is to be congratulated on producing a volume which is highly recommended, even at £32.95!

D. Littlewood

Papers for publication and all editorial communications should be addressed to the Editor, University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW; business communications to the publishers: Professional & Scientific Publications Ltd, BMA House, Tavistock Square, London WC1H 9JR.

The GUIDE TO CONTRIBUTORS can be found on pages viii, x & xii of the advertisement section of this issue.

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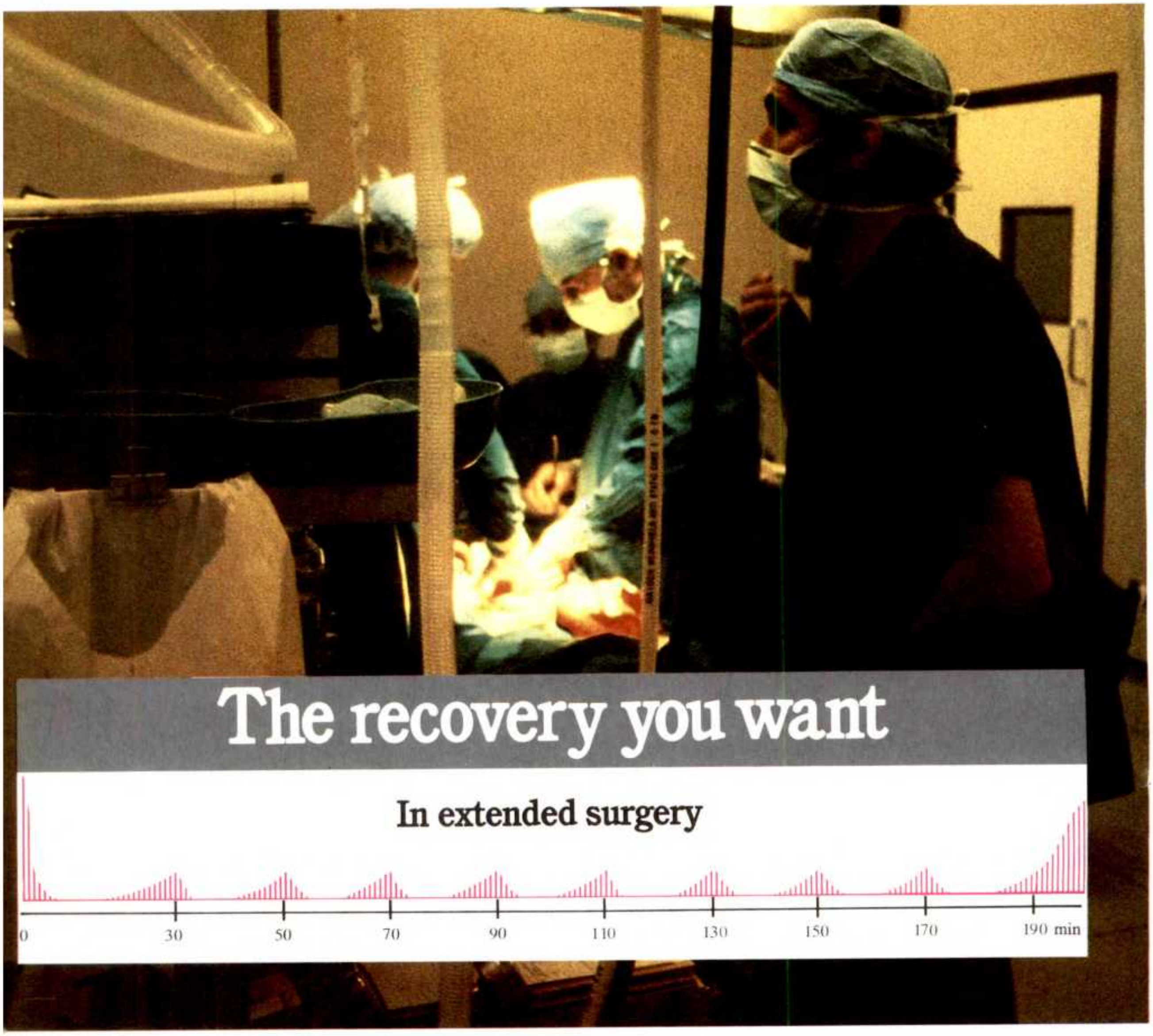

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1. Data on file, Wellcome, 1987.
2. Yate, P.M. *et al.* (1986), *Br. J. Anaesth.*, **58**, 112 S.

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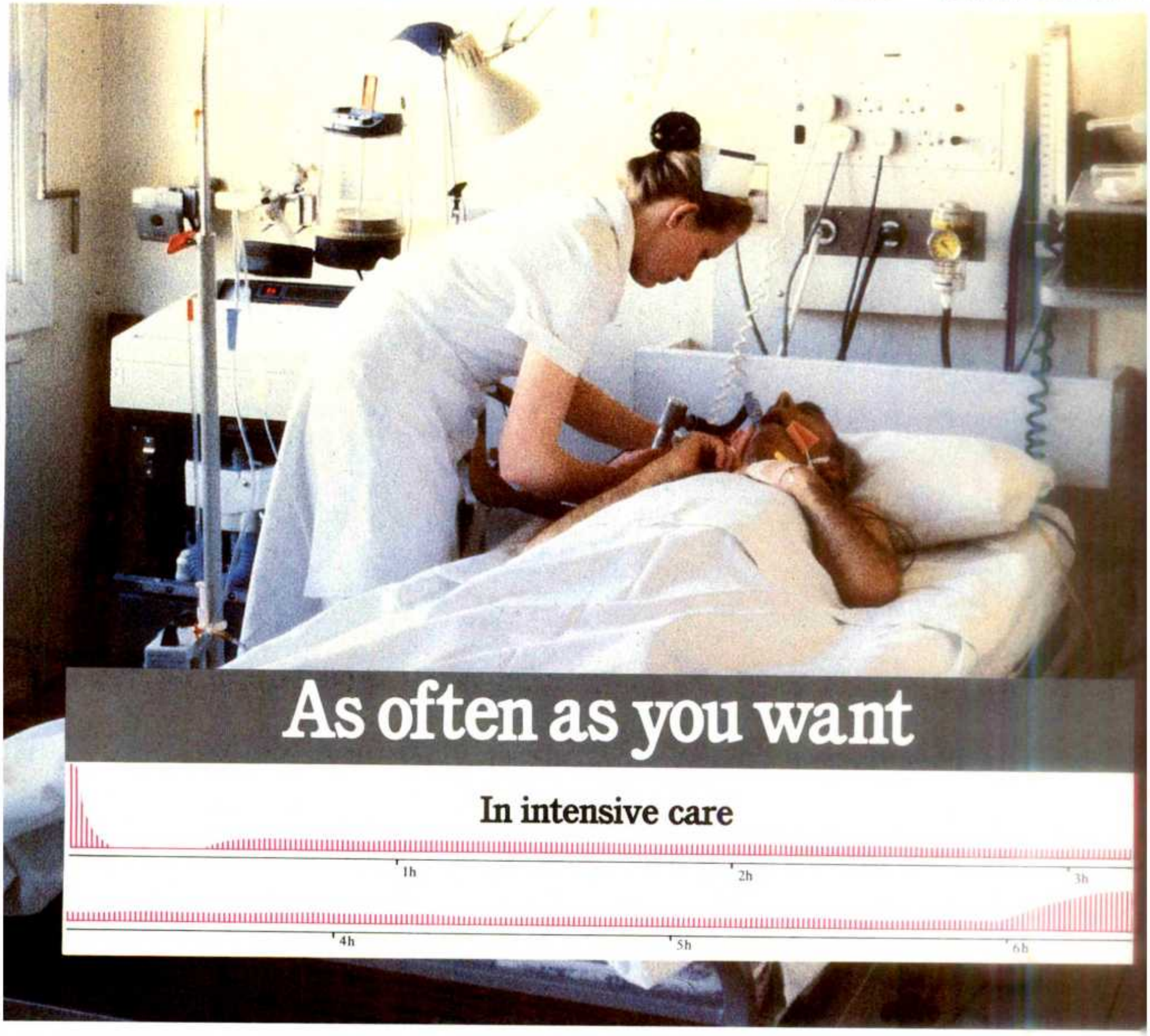

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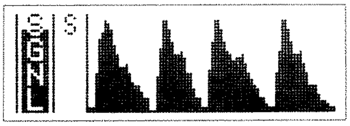

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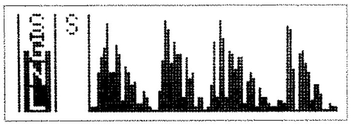

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[1] Costarino AT, Davis DA, Keon TP: Falsely normal saturation reading with the pulse oximeter. *Anesthesiology* 67:830–831, 1987. [2] Hanowell L, Eisele JH Jr, Downs D: Ambient light affects pulse oximeters, Correspondence. *Anesthesiology* 67:864–865, 1987. [3] Swedlow DB, Running V, Feaster SJ: Correspondence. *Anesthesiology* 67:865, 1987. [4] Block FE Jr: Interference in a Pulse Oximeter from a Fiberoptic Light Source. *Journal of Clinical Monitoring,* July 1987, pp 210–211. [5] Brooks T, Paulus D, Winkle W: Infrared Heat Lamps Interfere with Pulse Oximeters. *Anesthesiology* 61:630, 1984.

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Thursday, March 3, Stracathro:	Registrar's Prize Papers
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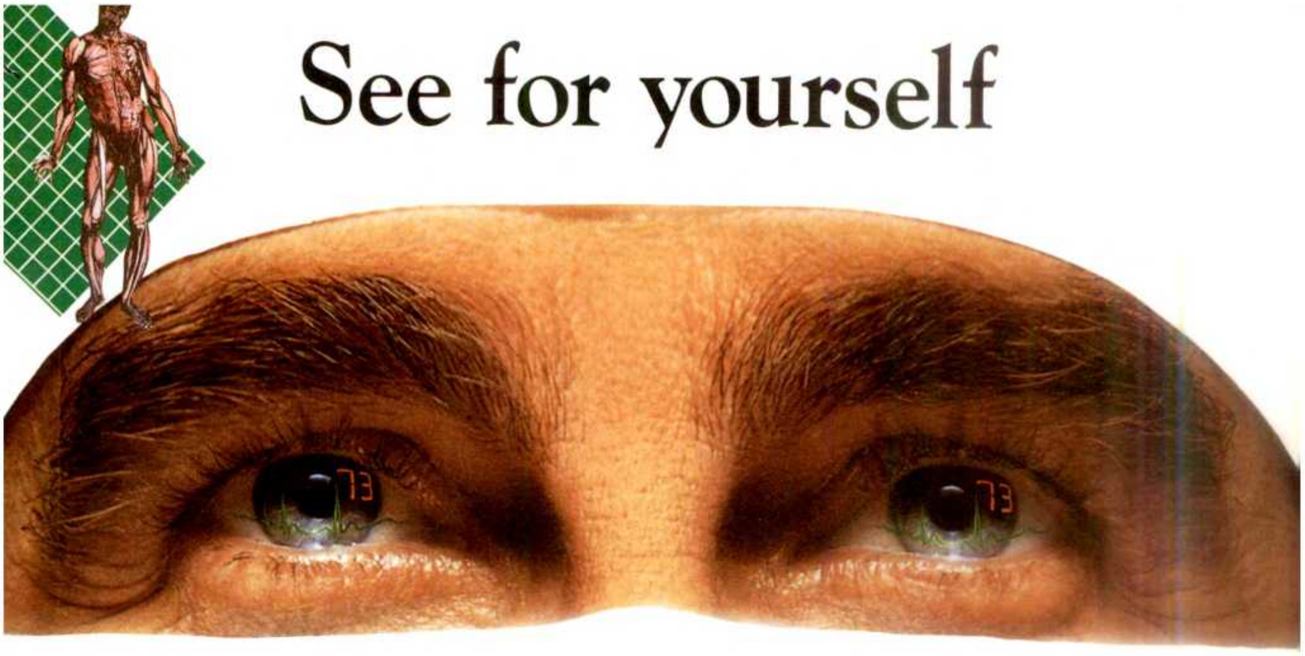

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Introduction (not headed)
Methods
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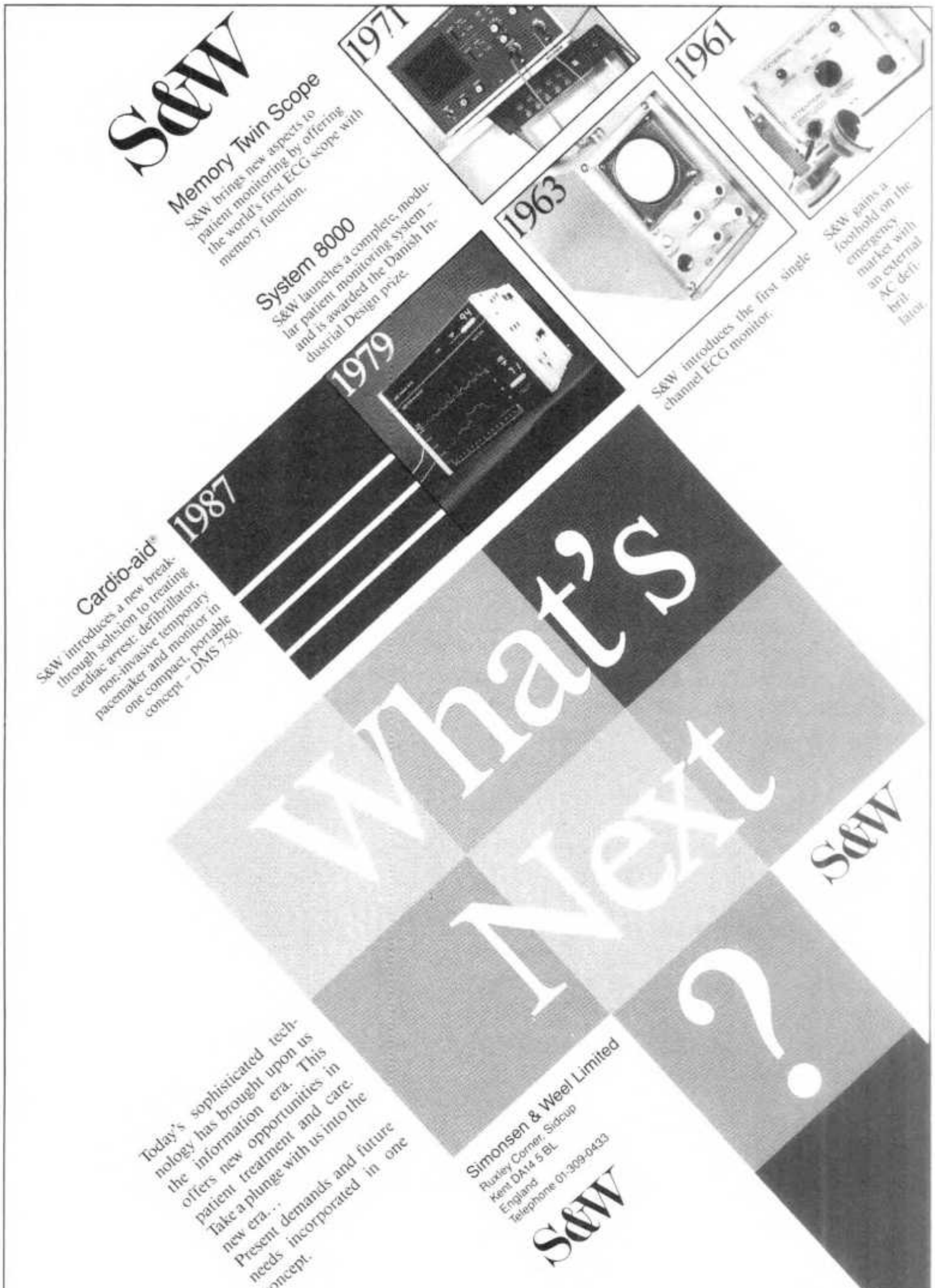

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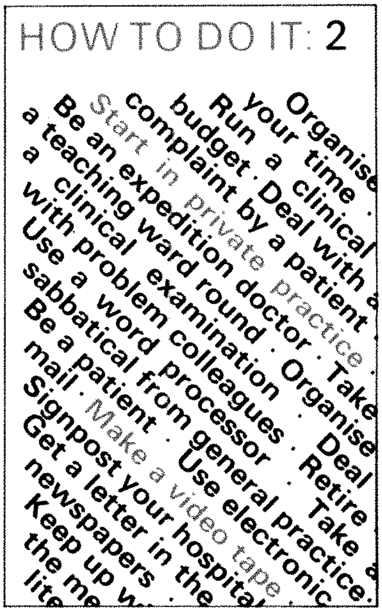

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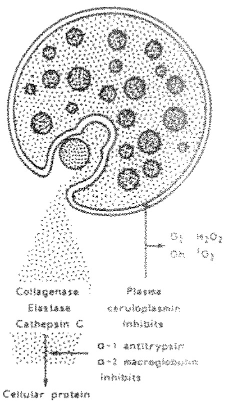

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BRITISH JOURNAL OF ANAESTHESIA

VOLUME 60, No. 4 MARCH 1988

EDITORIAL

ANAESTHESIA IN THE UNDERGRADUATE MEDICAL CURRICULUM

British Universities and their medical schools, struggling to retain viability in the face of cuts in funding, are aware of the need to rationalize every department involved in the expensive process of teaching medical students. We, the teachers, must be prepared to justify our staffing and educational programmes.

Should anaesthesia be taught to medical students? Currently, in Medical Schools in the U.K., the duration of student attachments to departments of anaesthesia varies from 0 to 4 weeks. Why is there such disparity? Clinical instruction certainly seemed to be essential in the days when the majority of anaesthetics were given by medical students, and yet at that time anaesthetic teaching was minimal. Anaesthesia is now a complex and highly technical subject and tends to be regarded as a postgraduate specialty. If it is accepted that the medical student does not need to be able to give an anaesthetic, what role does the anaesthetist have in teaching undergraduates?

A survey [1] of medical student opinion from three London Medical Schools concerning a number of specialties did not give a very encouraging picture of the importance of anaesthesia in the medical curriculum. The following is an extract from this paper identifying the opinion of anaesthesia:

> "Anaesthetics—Compared with the other specialties anaesthetics was seen to be taught in the most boring and irrelevant way; but it was most scientific and precise; anaesthetists were least likely to abuse their power; students taking up anaesthetics training were running away from practising real medicine; anaesthetists got less satisfaction from their work than other doctors; anaesthetics was the least important part of the curriculum; anaesthetics did not allow for the development of rewarding relationships; anaesthetists' patients were the least interesting to work with; anaesthetics was the least fraudulent and hence most effective; yet most medical students report that their anaesthetic training has been valuable".

It is to be hoped that a national survey might reveal a different perspective, reflecting a more enlightened approach to the teaching of anaesthesia in many provincial medical schools.

Certainly, the teaching of anaesthesia *per se* is the least important aspect of the anaesthetist's contribution to the general training of a good doctor. The subjects ideally taught by our specialty include cardiopulmonary resuscitation, care of the critically ill patient, preoperative evaluation and preparation of the patient for surgery, clinical pharmacology, pain therapy and, last, anaesthesia itself.

Cardiopulmonary resuscitation. As a result of the activities of several enthusiastic societies (the most notable of which are BASICS, and the Resuscitation Council: UK), there is now public awareness of the methods and values of resuscitation. The recommendations of the General Medical Council [2] state that on qualification the graduate should have developed "the professional skills necessary to deal with common medical emergencies". They state that instruction should be given in resuscitation and in the care of the unconscious patient and that "These subjects should be taught by specific periods of instruction and clinical attachment to a department of anaesthesia or in collaboration between anaesthetists and other specialists". Consequently, the arguments that resuscitation is often unsuccessful, inappropriate or provides ethical dilemmas [3, 4], although valid as discussion points, are not an issue in the education of medical students. The present situation is that in newly qualified doctors the public *expects* and the General Medical Council *demands* a reasonable level of expertise in resuscitation.

In 1982 it was shown that no more than 50 % of newly qualified doctors believed that they could manage an unconscious patient competently, whilst even fewer thought themselves competent in cardiopulmonary resuscitation [5]. After formal testing of newly qualified graduates it was apparent that some of those who thought they were competent merely felt that they would be able to cope when the time came. Studies in the U.S.A. found that only 29 % of junior doctors could perform basic life support [6], and in Addenbrookes Hospital, Cambridge, only 8 % of junior doctors could manage a cardiopulmonary arrest adequately [7]. Another survey [8] showed that, although 55 % of new doctors were able to perform external cardiac massage and mouth-to-mouth ventilation, none would have achieved a pass in the advanced life support examination in the U.S.A. [9]. This led to several leading articles, which revealed a consistent theme that resuscitation equipment must be available widely and doctors must be able to use it [10–12].

The principles of basic life support (mouth-to-mouth, or mouth-to-nose ventilation, and cardiac massage) can be demonstrated well with a simulated model. Such models can be used also to demonstrate advanced life support including cardiac massage, tracheal intubation, i.v. cannulation, recognition of arrhythmias and defibrillation. The models available provide an assessment of the adequacy of the student's performance. Although the models are very good, the anaesthetist can also offer practice in managing i.v. cannulation and airway management in the anaesthetized patient. It is unreasonable to practise mouth-to-mouth ventilation on patients, but the opportunity to master mask inflation, airway control and tracheal intubation is unrivalled. Quiet times in the operating theatre can also be used to reinforce the theoretical basis of resuscitation and the application of defibrillation can be demonstrated in the cardiac surgical theatre. Cardiac surgery is not normally included in the undergraduate curriculum, but a day allocated to the cardiac theatre during an anaesthetic attachment may be the only opportunity that a student has of observing a fibrillating heart and how the defibrillator works. Students should also be encouraged to join the resuscitation team at real cardiac arrests.

Care of the critically ill patient. Care of such patients includes acute emergencies in the casualty department, and those with multiple organ failure in intensive care units. Care of these patients crosses the boundaries of many medical and surgical specialties where the anaesthetist becomes the central co-ordinator of management. Students have the opportunity to become familiar with the priorities of treatment in the acute setting and to obtain an overall view of multiple pathology. Students are introduced to intensive therapy units, locations which are often daunting to (and thus avoided by) preregistration house officers. The recognition and management of acute and chronic ventilatory failure associated with surgery, trauma, chronic lung disease, neurological disease and self-induced poisoning are particularly relevant.

Preoperative evaluation and preparation of the surgical patient. The preparation of surgical patients for anaesthesia and surgery is an important part of the work of preregistration house officers. The most appropriate person to teach the evaluation and perioperative management of coexisting medical conditions is undoubtedly the anaesthetist. The importance of concurrent drug therapy (e.g. antihypertensive and antianginal drugs, hypoglycaemic agents, anticoagulants) and possible drug interactions with agents used during anaesthesia may possibly be overlooked by other disciplines. The relevance of preoperative biochemical and physiological assessment are also important. A knowledge of anaesthesia also allows the house officer to give the patient a more informed explanation of procedures and risks associated with surgery.

Clinical pharmacology. The anaesthetist is fortunate in having at his disposal rapidly acting drugs with actions that the student can instantly observe; thus the teaching of preclinical pharmacology can be reinforced. How better to appreciate the differences between depolarizing and non-depolarizing neuromuscular blocking agents than to observe their clinical effects and highlight them by peripheral nerve stimulation? How better to appreciate the ventilatory depressant properties of opioids than to observe the effect of an i.v. dose? The premise that a student is unlikely to have to give anaesthetics is not borne out in the case of local anaesthetics: although surgeons may describe the appropriate anatomy for a local anaesthetic block, the pharmacology, toxic dosages and treatment of side effects and overdosage are covered more thoroughly by the anaesthetist. The use and dangers of sedative drugs, such as benzodiazepines and their interactions with opioids, can be illustrated before the house officer uses them, possibly unsupervised. The use of intra-arterial monitoring can be used to illustrate vividly the effects of a variety of drugs, but especially of sympathomimetic amines for inotropic or chronotropic augmentation of cardiac action, and the restoration of arterial pressure and systemic blood flow.

Pain therapy. The scope of this subject covers both acute, postoperative pain treatment and the diagnosis and management of chronic pain; all subjects which the General Medical Council considers to be an important part of medical undergraduate education. The anaesthetist is able to give the student the broadest possible view of pain therapy. The advantages and disadvantages of different routes of administration of opioids can be demonstrated and the advantages and disadvantages of regional blockade illustrated. More importantly, the effectiveness and problems of management, and occurrence of side effects can easily be demonstrated to reinforce the student's memory.

Anaesthesia. Although we have implied that this is the least important aspect of our teaching role, it is nonetheless sensible that the student has some insight to the intricacies of the specialty, if only to have respect for the drugs used, the procedures undertaken and for the problems encountered. Patients undergoing general anaesthesia provide excellent opportunities for the student to appreciate and apply the management of the unconscious patient. Perhaps surprisingly, skill in communication was highlighted in a prize essay by one of our medical students as an important aspect of her experience of anaesthetic teaching: in addition to good communication with patients in a limited time, she also cited its importance in achieving good rapport with the surgical team to provide optimum outcome for the patient.

Competition for time in the undergraduate medical curriculum is always fierce. An introductory course of lectures complemented by audiovisual aids and practical experience on resuscitation models ensure a theoretical grounding. Personalized programmes, such that a student receives individual tuition from anaesthetists in the operating theatre and on the wards, maximize experience in many practical procedures and illustrate a multitude of physiological, pharmacological and pathological processes. Only one-to-one teaching provides this optimum opportunity for thorough explanations and a full understanding of these processes. This can be achieved only by the unfailing enthusiasm and co-operation of our university and health service colleagues. In our view, it is unrealistic to expect such a course to cover the range of topics and experience outlined above in less than 4 weeks.

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PATIENT-CONTROLLED ANALGESIA WITH EXTRADURAL MORPHINE OR PETHIDINE

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SUMMARY

Two groups of patients were allowed to self-administer morphine (n = 17) or pethidine (n = 15) extradurally after abdominal surgery, for a mean period of 16 h. Bolus increments of morphine 1 mg or pethidine 20 mg were administered by programmable pump. Pain relief from extradural patient-controlled analgesia (PCA) was excellent in all but two patients in the morphine group. Pain relief was not qualitatively different between the two groups. No clinical respiratory depression was seen. The average consumption of extradural morphine was 0.52 ± 0.29 mg h^{-1} (range 0.19–1.04 mg h^{-1}) and of pethidine 18.0 ± 8.1 mg h^{-1} (5.8–35.4 mg h^{-1}). This yields an equianalgesic dose relationship of 1:35. Morphine consumption was more irregular than pethidine consumption. Morphine and pethidine plasma concentrations measured during PCA were well below the reported minimum analgesic plasma concentrations in most cases. Several patients, particularly in the pethidine group, tended to increase their opioid consumption during PCA. This could be explained by an increasingly smaller fraction of the pethidine bolus being absorbed to the subarachnoid space during frequent repetitive dosing. The large inter-individual variation in consumption makes it impossible to recommend a standard dose of extradural morphine or pethidine for analgesia of predictable duration and with a minimum of adverse effects.

With patient-controlled analgesia (PCA), the patient is allowed to self-administer small bolus increments of an analgesic drug by means of a programmable pump device. The method has proved to be effective in relieving postoperative pain [1–6]. A wide variety of analgesic drugs have been used, mostly by the i.v. route, but also i.m. [7].

The extradural administration of opioids has been used clinically since 1979 to relieve both acute and chronic pain [8]. Several adverse effects, including respiratory depression, urinary retention, itching, nausea and vomiting have been reported following extradural morphine [9]. Some of the adverse effects are elicited at supraspinal centres to which the drug is thought to be transported with cerebrospinal fluid (CSF) bulk flow [10, 11]. Absorption across the dura from the extradural space and removal from CSF is slower for morphine than for pethidine, probably because of differences in lipophilicity [12]. Theoretically, the risk of eliciting supraspinal adverse effects should be smaller when using a more lipophilic compared with a hydrophilic drug. Extradural morphine has been reported to be longer acting than extradural pethidine, fentanyl and methadone [13], but the relative efficacy and adverse effects of different opioids are largely unknown.

The purpose of this study was to combine the concept of patient-controlled analgesia with that of extradural administration of opioids in order to compare two drugs (morphine and pethidine) with different physicochemical properties and receptor binding characteristics.

PATIENTS AND METHODS

The study was approved by the ethics committee of the Medical Faculty of Uppsala University.

Thirty-two patients undergoing major abdominal surgery gave their informed consent to

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participate in the study. A majority of the patients suffered from inflammatory bowel disease or peptic ulcer. None had signs or symptoms of renal or hepatic dysfunction, psychiatric disease or a history of drug or alcohol abuse. Individual patient data are shown in tables I–III.

After an overnight fast, all patients were premedicated with diazepam 10–15 mg by mouth and atropine sulphate 0.5 mg i.m. Anaesthesia was induced with thiopentone and a single dose of droperidol 5 mg. Orotracheal intubation was performed after pancuronium bromide 0.1 mg kg^{-1}. An extradural catheter was placed at the lower thoracic or lumbar level. The lungs were ventilated mechanically with 30% oxygen in nitrous oxide. Additional increments of pancuronium 1–2 mg were given as required. Intraoperative analgesia was provided with increments of fentanyl in 0.1–0.2 mg doses to suppress signs of surgical stress.

When the surgical procedure was completed, the trachea was extubated and the patient transferred to a recovery room where s/he remained overnight. Routine observations included checks, at least every 60 min, of arterial pressure, heart rate and ventilatory frequency.

When the patient requested pain relief a programmable PCA-pump (Prominject, Pharmacia, Sweden) was connected to the extradural catheter. The PCA pump was programmed to deliver incremental doses of 1 mg of preservative-free morphine hydrochloride 1 mg ml^{-1} (17 patients), or 20 mg of pethidine hydrochloride 25 mg ml^{-1} (15 patients), with a minimum time interval of 30 min between doses. Patient-controlled administration commenced in the afternoon after surgery and continued until the following morning. No other analgesics were administered during the period of PCA. However, those who experienced insufficient pain relief from extradural PCA were offered i.v. PCA.

The hourly consumption of morphine or pethidine during PCA was recorded, as were the patients' average time intervals between doses.

Pain was assessed by means of a visual analogue scale (VAS) consisting of a horizontal 100-mm line marked "No pain" at its left end and "Worst imaginable pain" at its right end. The patients were not shown their previous ratings. Pain was assessed before the start of PCA, twice during the period 1–4 h after the start, and when PCA was discontinued.

Pain relief was calculated as percent reduction of pain:

$$\frac{\text{VAS before PCA} - \text{VAS during PCA}}{\text{VAS before PCA}} \times 100$$

On the 3rd or 4th day after operation, the patient was asked to give an overall assessment of the pain relief from extradural PCA on a four-point scale ranging from "insufficient" to "very good" analgesia. Reports of adverse effects listed in table IV were obtained by direct questioning.

Venous blood samples for drug assay were collected during the PCA period at times not less than 15 min after a dose. The plasma was separated and frozen at −20 °C until analysed. Morphine and pethidine were assayed with gas–liquid chromatography using electron-capture detection [14, 15]. The limit of detection of the method was 1 ng ml^{-1} for morphine and 5 ng ml^{-1} for pethidine.

Student's t test for independent means or the chi-square test were used for comparison of the groups; $P < 0.05$ was considered to represent statistical significance.

Dose administration patterns were analysed individually with respect to regularity/irregularity. The coefficient of variation of the time intervals between consecutive doses was calculated for each individual using the equation:

$$\text{Coefficient of variation (\%)} = (\text{SD (dose interval)} / \text{Mean (dose interval)}) \times 100.$$

RESULTS

Clinical course

The clinical course of all patients was uncomplicated. There were no significant differences between the morphine and pethidine groups with regard to age, sex, weight, body surface area, duration of operation, consumption of fentanyl during operation, intraoperative blood loss or between these factors and postoperative requests for analgesia (table I).

There were no significant changes in, or differences between the groups with regard to breathing frequencies. No frequencies less than 12 b.p.m. were recorded during PCA.

Disorders of micturition could not be detected since most of the patients had urinary catheters.

TABLE I. *Individual data of the patients in the morphine and pethidine groups. Sex, age, body weight, body surface area (BSA), duration of operation, peroperative consumption of fentanyl, peroperative blood loss and level of extradural catheter*

No.	Sex	Age (yr)	Body wt (kg)	BSA (m^2)	Duration of op. (min)	Fentanyl consump. ($mg\ h^{-1}$)	Blood loss (ml)	Catheter level
Morphine group								
1	M	44	65	1.84	140	0.34	450	L2–3
2	M	56	79	2.03	300	0.30	3300	T10–11
3	F	25	58	1.64	90	0.40	500	T11–12
4	M	35	97	2.15	120	0.45	450	T11–12
5	F	29	56	1.67	225	0.29	800	T11–12
6	F	29	56	1.69	175	0.14	1100	T12–L1
7	F	48	68	1.80	105	0.34	500	T11–12
8	M	23	84	2.09	145	0.21	400	T10–11
9	M	20	48	1.63	165	0.22	1100	T11–12
10	F	36	65	1.75	190	0.32	1500	T11–12
11	F	42	103	2.11	185	0.16	600	L2–3
12	F	19	45	1.51	145	0.17	950	T11–12
13	F	22	55	1.70	90	0.27	300	T11–12
14	F	64	57	1.67	145	0.37	750	T10–11
15	F	32	56	1.57	150	0.20	300	T11–12
16	F	35	77	1.89	125	0.22	150	T11–12
17	F	23	51	1.55	185	0.19	2400	T10–11
Mean		34.2	65.9	1.78	158	0.27	915	
SD		13.0	16.8	0.20	52	0.09	823	
Pethidine group								
18	M	33	91	2.10	165	0.29	1700	L2–3
19	F	36	76	1.86	170	0.28	200	L2–3
20	M	28	69	1.88	235	0.18	1700	L2–3
21	F	44	58	1.68	180	0.20	1400	T11–12
22	F	24	46	1.56	190	0.19	1000	T12–L1
23	M	41	74	1.89	185	0.39	2600	T7–8
24	M	29	63	1.63	135	0.22	2700	T12–L1
25	F	21	58	1.60	165	0.18	400	T11–12
26	F	22	56	1.58	140	0.21	900	T11–12
27	F	42	57	1.64	225	0.21	1600	T11–12
28	M	24	54	1.62	140	0.34	250	T11–12
29	F	52	60	1.69	140	0.17	500	T11–12
30	F	35	54	1.61	120	0.25	400	T11–12
31	F	45	60	1.68	120	0.15	300	T11–12
32	M	34	62	1.82	185	0.19	3300	T11–12
Mean		34.0	62.5	1.72	166	0.23	1263	
SD		9.4	11.1	0.15	35	0.07	995	

Self-administration of morphine

PCA lasted for a mean period of 16.7±2.6 h in the morphine group (table II). Two of the 17 patients (Nos 16 and 17) experienced insufficient pain relief despite having administered three and four doses of morphine, respectively. They were offered i.v. PCA with morphine, and obtained satisfactory relief.

The remaining 15 patients were satisfied with the pain relief from extradural morphine, and consumed 0.52±0.29 mg h^{-1} (range 0.19–1.04 mg h^{-1}).

Pain assessment on the 100-mm VAS scale before PCA averaged 52.8±13.8 mm. Pain relief at the end of the PCA period was 71.1±27.7% reduction of pain. Maximum pain relief recorded was 73.1±27.1%.

Morphine consumption tended to follow an irregular pattern. The mean time interval between doses was 166±107 min. The mean coefficient of variation of the time intervals was 60.9±26.2%. The time intervals did not change in any uniform pattern during the PCA period.

TABLE II. *Data from the PCA period in the morphine group. Opioid consumption during PCA, duration of the PCA period, mean (± SD) time between doses, plasma concentrations of opioid, pain assessment on a visual analogue scale (VAS) before PCA, maximal pain relief recorded and pain relief at the end of the PCA period as % reduction of initial pain*

No.	PCA consump. (mg h^{-1})	PCA duration (h)	Time between doses (min)	Plasma concn (ng ml^{-1}) < 1 (*n*)	1–10.0 (*n*)	10.1–20.0 (*n*)	VAS before PCA (mm)	Reduction of pain: Maximal	At end of PCA
1	0.42	16.6	142±115	3	1	0	50	30	22
2	0.19	21.6	324±216	3	2	0	40	73	73
3	0.22	18.1	275±142	2	0	1	33	88	88
4	0.59	17.0	105±75	2	0	0	31	61	61
5	0.75	15.9	79±37	0	2	0	41	39	39
6	0.15	19.6	392±72	4	0	0	50	100	100
7	0.80	12.5	75±28	0	3	1	54	11	11
8	0.64	17.2	94±47	0	3	0	68	99	99
9	0.83	16.8	72±45	0	2	0	44	89	66
10	0.22	18.3	275±287	2	2	0	66	95	95
11	0.29	17.3	207±136	1	2	0	52	67	67
12	0.90	17.8	57±33	0	0	4	73	82	82
13	1.04	16.3	58±47	1	2	2	66	97	97
14	0.33	15.3	184±27	1	1	2	73	86	86
15	0.38	10.6	159±166	2	0	0	51	80	80
Mean	0.52	16.7	167				52.8	73.1	71.1
SD	0.29	2.6	107				13 8	27.1	27.7

Plasma morphine concentrations were low. Fifty-one blood samples were analysed for morphine and 21 of these were below the limit of detection (< 1 ng ml^{-1}), 20 were between 1 and 10 ng ml^{-1} and 10 were between 10.1 and 20 ng ml^{-1} (fig. 1).

In the postoperative questionnaires which were completed by those 15 patients who used only extradural PCA, 14 patients rated the pain relief as "very efficient" while one (No. 1) rated the analgesia as "slight". Three patients each experienced itching, nausea, vomiting and drowsiness.

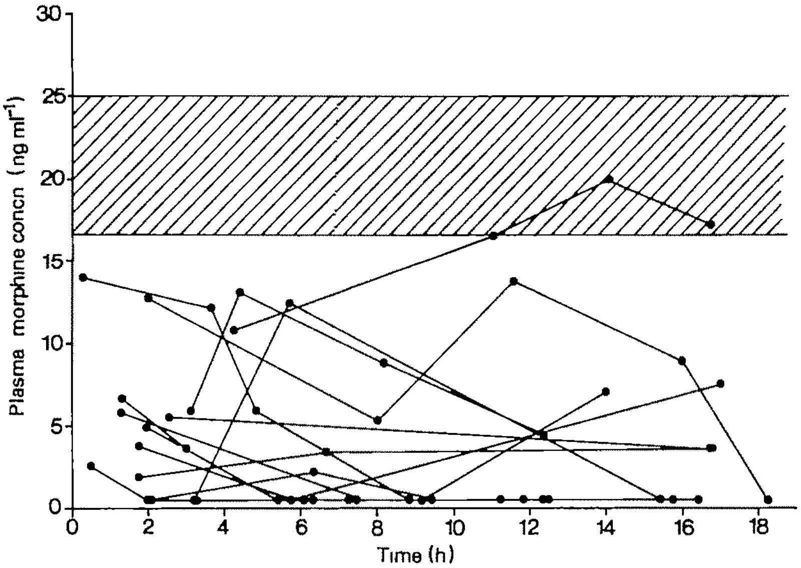

FIG. 1. Plasma morphine concentrations during extradural PCA with morphine. The shaded area is the reported mean ± SEM measured plasma morphine concentrations during i.v. PCA with morphine [3].

TABLE III. *Data from the PCA period in the pethidine group. (Details as table II)*

No.	PCA consump. (mg h^{-1})	PCA duration (h)	Time between doses (min)	Plasma concentration (ng ml^{-1})	Plasma concentration (*n*)	VAS before PCA (mm)	Reduction of pain: Maximal (%)	Reduction of pain: At end of PCA (%)
18	16.7	15.6	72±57	205±53	4	50	100	6
19	24.6	12.2	48±21	203±59	4	71	93	87
20	23.5	15.3	50±29	567±13	3	73	45	45
21	17.8	16.9	67±22	298±189	3	30	73	73
22	11.0	16.3	108±21	383±176	4	40	77	77
23	20.5	17.6	59±12	431±197	4	66	100	100
24	10.6	13.2	113±33	72±19	3	29	97	97
25	35.4	15.8	34±11	583±393	4	49	71	71
26	24.7	18.6	48±13	333±149	6	63	72	72
27	21.2	15.1	57±26	223±97	4	77	95	88
28	26.4	18.1	47±16	608±242	5	63	56	56
29	12.5	17.6	96±63	281±164	6	50	94	50
30	9.0	17.7	133±33	168±61	3	70	94	94
31	5.8	17.2	217±64	71±21	5	35	100	94
32	10.9	18.3	110±58	214±77	5	33	100	100
Mean	18.0	16.4	84	309		53.2	84.5	74.0
SD	8.1	1.9	48	174		16.9	17.7	26 0

No adverse effects were reported by four patients (table IV).

Self-administration of pethidine

PCA lasted for a mean period of 16.4±1.9 h in the pethidine group (table III). All 15 patients achieved subjectively satisfactory analgesia from extradural PCA. Consumption varied between 5.8 and 35.4 mg h^{-1} (mean dose of 18.0±8.1 mg h^{-1}).

Before PCA, pain assessment was 53.3±16.9 mm on the VAS scale. At the end of extradural PCA, the pain relief was assessed as 74.0±26.0 % reduction of pain, and maximum pain relief recorded was 84.5±17.7 %.

Pethidine consumption tended to be more regular than morphine consumption. The mean

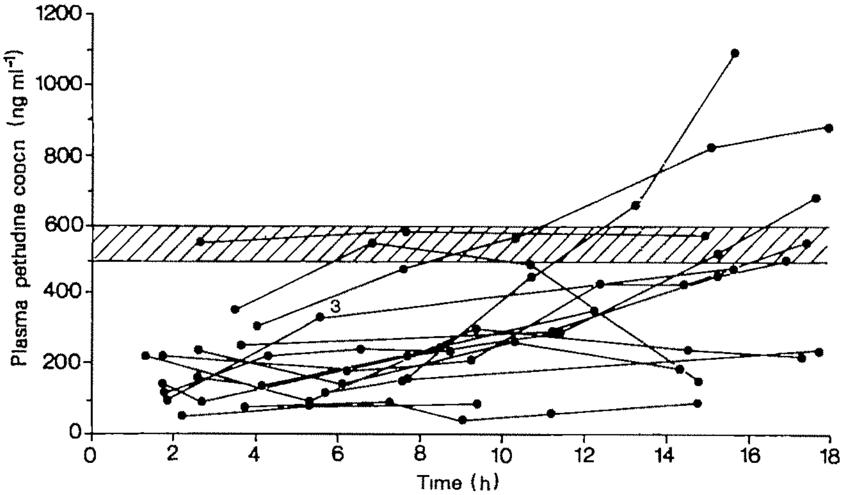

FIG. 2. Plasma pethidine concentrations during extradural PCA with pethidine. The shaded area is the reported mean±SEM measured pethidine plasma concentrations during i.v. PCA with pethidine [2].

TABLE IV. *Number of patients reporting subjective adverse effects from extradural PCA in the postoperative questionnaire*

Effect	Morphine group ($n = 15$)	Pethidine group ($n = 15$)
Nausea	3	1
Vomiting	3	1
Drowsiness	3	6
Accommodation problems	2	1
Dryness of mouth	5	7
Sense of happiness	0	4
Unpleasant dreams	1	1
Pleasant dreams	0	1
Itching	3	0
Leg numbness	0	1
No adverse effects	4	4

time interval between self-administered doses was 84 ± 47 min, and the mean coefficient of variation of the time intervals between doses was $39.3 \pm 17.5\%$ which was significantly smaller compared with the morphine group. Several of the patients tended to increase their pethidine consumption during the PCA period.

Mean plasma concentrations of pethidine in 15 patients varied between 71 and 567 ng ml^{-1}, and averaged 309 ± 174 ng ml^{-1} (fig. 2).

All patients rated the pain relief from extradural PCA with pethidine as "very efficient" in the postoperative questionnaire. Four patients did not report any adverse effects. One patient experienced nausea, one vomiting and one vivid dreams. Four patients experienced a sense of happiness and six reported being drowsy. One patient reported leg numbness (patient No. 25, who consumed 35.4 mg h^{-1}). No patient reported itching (table IV).

DISCUSSION

Analgesic effect, dose requirements and adverse effects

Using extradural PCA, all patients but two were able to achieve adequate analgesia in the immediate postoperative period. There was no significant difference in drug induced pain relief between morphine and pethidine. No clinical respiratory depression occurred, in spite of the relatively large doses consumed by some patients.

The adverse effects elicited were minor, and did not affect the popularity of the method. The incidence of adverse effects was similar in the morphine and pethidine groups.

One of the pethidine patients reported numbness of the legs, which was noted during the PCA period and disappeared rapidly. The numbness might have been caused by the weak local anaesthetic action of pethidine [16].

In earlier studies [2, 3] i.v. PCA was used after major abdominal surgery when patients consumed morphine 2.6 ± 1.2 mg h^{-1} and pethidine 26 ± 10 mg h^{-1}, respectively. Thus the extradural morphine consumption in the present study was only 20% of the i.v. consumption, whereas the extradural pethidine consumption was 70% of the i.v. consumption (table V). The differences between i.v. and extradural consumptions for both drugs are statistically significant ($P < 0.001$ for morphine and $P < 0.02$ for pethidine).

Analgesia from both morphine and pethidine has been shown to be longer acting when the drugs are administered extradurally compared with systemic administration [17–19]. Morphine is longer acting than pethidine when administered extradurally in doses of 6 mg and 60 mg, respectively [13]. The equianalgesic dose relationship

TABLE V. *Comparison of doses required (mean ± SD) to achieve postoperative analgesia with PCA using morphine and pethidine via the i.v. and extradural routes*

	Route of administration	
	I.v.	Extradural
Morphine consumption (mg h^{-1})	2.6 ± 1.0	0.52 ± 0.29
Relative consumption (extradural morphine = 1)	5	1
Pethidine consumption (mg h^{-1})	26 ± 10	18.0 ± 8.1
Relative consumption (extradural morphine = 1)	50	35

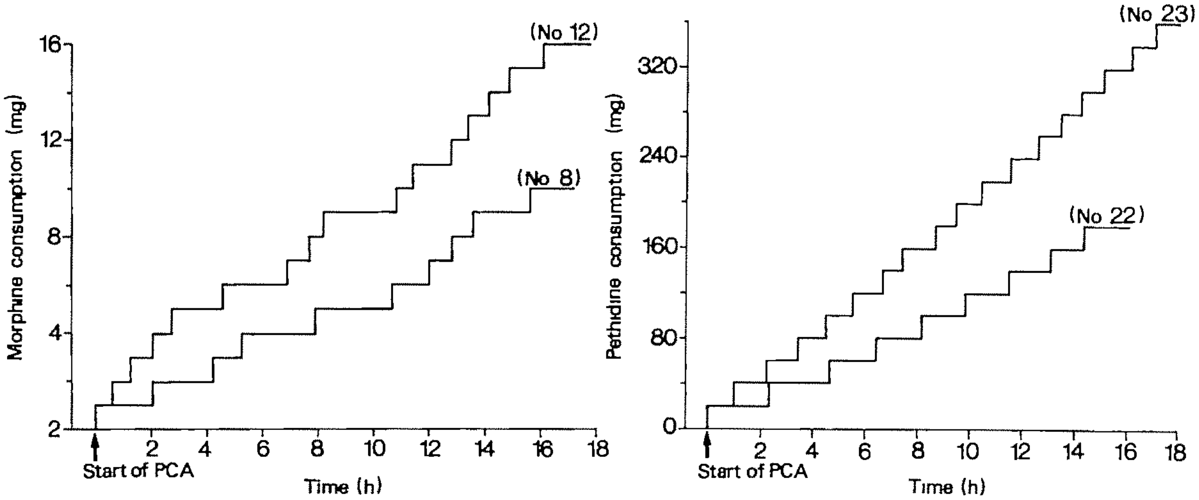

FIG. 3. Accumulated consumption of morphine and pethidine during extradural PCA in two patients from the morphine group (Nos 8 and 12) and two from the pethidine group (Nos 22 and 23).

between systemic morphine and pethidine is known to be 1:10 [20]. The present study has revealed a relationship of 1:35 after extradural administration. This reflects the closeness of the site of administration to the opioid receptors in the spinal cord, and differences in CSF kinetics and in opioid receptor affinities [21].

The doses of extradural morphine necessary to produce analgesia after abdominal surgery have been reported to be 2–10 mg, with a duration ranging from 4 to 24 h [13, 22–24]. The average consumption of morphine during PCA in the present study corresponded to a dose of 12 mg during a 24-h period. The morphine consumption varied five-fold, as did the pethidine consumption. The average consumption of pethidine during PCA corresponded to a dose of 430 mg during a 24-h period. The doses of pethidine consumed during extradural PCA were in accordance with the reported doses of 50–100 mg required to achieve analgesia after abdominal surgery with a reported duration of analgesia ranging from 2 to 10 h [13, 25, 26]. Although a part of this variability may be accounted for by the pharmacokinetic properties of the drugs, it emphasizes further the differences between individuals in pain perception [27]. The large inter-individual variation makes it impossible to recommend a standard dose of extradural morphine or pethidine for analgesia of predictable duration and with a minimum of adverse effects. Patient-controlled analgesia via the extradural route thus provides an alternative way to give an individualized pain therapy.

Consumption patterns

The consumption patterns during PCA differed in the morphine and pethidine groups. The accumulated doses of two typical patients from the morphine and two from the pethidine group during the PCA period (fig. 3) illustrate that patients self-administering morphine demanded doses at more irregular intervals, as is shown also by the more variable time intervals between doses.

This difference probably reflects differences in CSF kinetics between the two drugs. Morphine is absorbed slowly across the dura, and maximum CSF concentrations are found 60–90 min after extradural injection, whereas pethidine passes the dura more rapidly with maximum CSF concentrations appearing 15–30 min after injection [12].

Because of its lipophilicity, pethidine reaches the receptor sites in the spinal cord more quickly than morphine. This is confirmed by the shorter onset of action of extradural pethidine compared with extradural morphine [22, 26]. The slow onset of action of extradural morphine is therefore a disadvantage when the drug is administered by means of PCA.

It is possible that the incremental bolus size of the drugs may influence the total amount consumed during PCA. This is suggested by a pilot study in which seven patients were allowed to self-administer 10-mg doses of pethidine extradurally and consumed only 9.7 ± 5.2 mg h^{-1} following abdominal surgery [28]. These patients were significantly older ($P < 0.05$) than the patients in the present study, which may account in part for the lower consumption.

CSF and plasma concentrations

The tendency among some of the patients in the pethidine group to increase their consumption during extradural PCA, in addition to the high opioid consumption of some of the patients, may also indicate real differences in single dose and multiple dose kinetics. Only a small fraction, approximately 4%, of an extradural single bolus dose is absorbed to the subarachnoid space [12]. The main fraction of the bolus dose is absorbed rapidly. Because of the large differences in the volumes of distribution [3, 29–31], the concentrations in CSF exceed those in plasma many times. The concentration gradients that result favour the systemic absorption of a second extradural dose. According to this hypothesis, as CSF concentrations gradually increase during repetitive doses, a successively smaller fraction of each dose would be absorbed to the subarachnoid space.

The plasma concentrations were low in the morphine group, and nearly all the measured values were below the reported minimum analgesic concentration of 16 ± 6 ng ml^{-1} [3] and 20–40 ng ml^{-1} [32]. It therefore seems safe to conclude that systemic morphine does not contribute to the analgesia.

Minimum effective plasma concentrations of pethidine after i.v. administration have been reported to be 400–500 ng ml^{-1} [2, 33], and this is higher than the mean pethidine plasma concentration achieved during extradural PCA. There was a trend towards increasing plasma concentrations during the PCA period, and systemic pethidine concentrations have probably contributed to the pain relief during the later part of the PCA period.

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DIFFERENTIAL EFFECTS OF NEUROMUSCULAR BLOCKING AGENTS ON SUXAMETHONIUM-INDUCED FASCICULATIONS AND MYALGIA

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SUMMARY

The effect of pretreatment with suxamethonium, gallamine or pancuronium on suxamethonium-induced fasciculations and myalgia was studied in a controlled, randomized and double-blind clinical trial. Both fasciculations and myalgia were assessed on a four-point rating scale. There was no significant correlation between fasciculations and postoperative muscle pain at 24, 48 or 72 h, and pretreatment with suxamethonium had no significant effect on fasciculations or myalgia. Gallamine had a more marked effect on fasciculations than pancuronium, and the decrease in the fasciculation score was statistically significant. In contrast, pancuronium had a greater effect on myalgia, and decreased postoperative muscle pain significantly at 24 and 48 h. These differences may reflect the differential activity of gallamine and pancuronium at the neuromuscular junction. Pretreatment had little or no effect on plasma potassium concentrations.

Suxamethonium commonly produces a number of undesirable effects, including muscle fasciculations, postoperative myalgia, and transient hyperkalaemia. These phenomena are commonly modified by pretreatment with small doses of non-depolarizing neuromuscular blockers. Suxamethonium produces muscle fasciculations by combining with neuronal cholinoceptors, causing prejunctional depolarization [1]; in these conditions, local axon reflexes initiate the release of acetylcholine from the terminals of motor units. The relationship between fasciculations and postoperative myalgia is controversial. Electromyographic evidence suggests that muscle pain is related to the rate of firing of motor units, but not to visible fasciculations [2]. Non-depolarizing myoneural blockers may modify fasciculations and muscle pain by preventing prejunctional depolarization and local axon reflexes, thus decreasing the rate of motor unit firing. They have multiple sites of action at the neuromuscular junction [3]; our previous studies suggested that gallamine has predominantly presynaptic effects, in comparison with pancuronium [4]. Pretreatment with these neuromuscular blocking drugs may therefore have differential effects on suxamethonium-induced fasciculations and myalgia. Other drugs, including small doses of suxamethonium itself, have also been used to prevent these complications [5]. However, the effectiveness of this procedure is a matter of controversy.

The effects of pretreatment on suxamethonium-induced fasciculations and myalgia have been widely studied. Nevertheless, few previous attempts have been made to analyse these phenomena in the context of a controlled clinical trial. In this study, we have assessed the effectiveness of pretreatment with suxamethonium, gallamine or pancuronium, in a controlled, randomized and double-blind clinical trial.

PATIENTS AND METHODS

Sixty identical 1.1-ml ampoules containing 0.9% saline, suxamethonium 10 mg ml^{-1}, gallamine 20 mg ml^{-1} or pancuronium 1 mg ml^{-1} were prepared by the Pharmacy Manufacturing Department of

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the Royal Liverpool Hospital. Similar doses of suxamethonium and gallamine have been used in many previous studies [5–7]. The doses of pancuronium 1 mg and gallamine 20 mg were considered to have equipotent effects on neuromuscular transmission. The ampoules were randomized, using random sampling numbers [8] by one of us (T.N.C.) who had no subsequent connection with the trial. The ampoules were sealed in sequentially numbered envelopes, and administered in this order to the patients who were entered to the trial.

Sixty female subjects (ASA grade I) aged 18–66 yr were studied. There was no significant difference between the ages and the body weights of the patients in the four treatment subgroups. All the patients had been admitted to hospital for elective plastic, ENT or gynaecological surgery. Informed consent was obtained, and the trial was approved by the local Ethics Committee. Patients were routinely premedicated with nitrazepam 10 mg during the previous evening and diazepam 5 mg three times on the day of surgery. Anaesthesia was induced with thiopentone 3 mg kg^{-1} i.v. and the sequentially numbered pretreatment was given. After 45 s a further dose of thiopentone 1 mg kg^{-1} i.v. and suxamethonium 1.5 mg kg^{-1} i.v. was administered. No other blocking agents were used, and patients were subsequently allowed to breathe spontaneously oxygen, nitrous oxide and enflurane from a Magill circuit. Blood was removed for the measurement of plasma potassium concentrations immediately before, and 5 min after, the induction of anaesthesia. The presence and degree of fasciculations were assessed on a four-point rating scale: 0 = no visible fasciculations; 1 = extremely fine muscular movements; 2 = minimal contractions of the trunk, face and extremities; 3 = vigorous contractions of the trunk, face and extremities.

Postoperative myalgia was assessed on a four-point rating scale at 24, 48 and 72 h, using the following criteria: 0 = no muscle pain; 1 = slight muscle pain; 2 = moderate muscle pain; 3 = severe muscle pain.

All the patients were ambulant within 24 h of surgery. The effects of the pretreatments on muscle fasciculations and postoperative myalgia were compared by Wilcoxon's signed rank test.

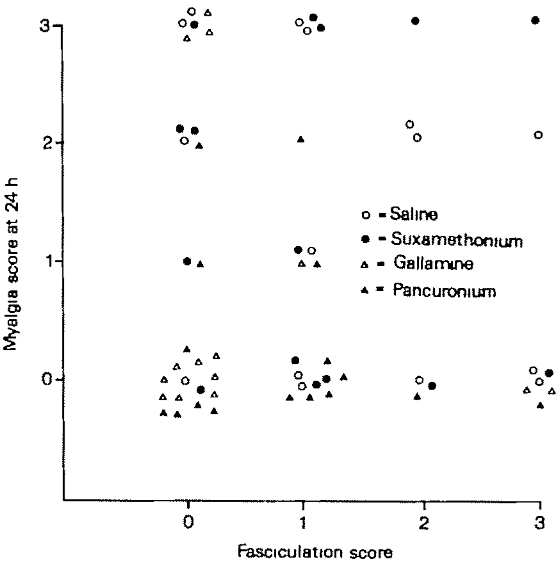

FIG. 1. Effect of saline, suxamethonium, gallamine and pancuronium on the fasciculation score and the myalgia score at 24 h. The correlation between these variables was not statistically significant ($r = -0.081$; $P \geqslant 0.05$).

TABLE I. *Effects of pretreatment with saline, suxamethonium, gallamine or pancuronium on fasciculations and postoperative myalgia. Figures represent median values (interquartile ranges). The data were compared by Wilcoxon's signed rank test.* *$P < 0.05$

Drug	Fasciculation score	Myalgia score 24 h	Myalgia score 48 h	Myalgia score 72 h
Saline	1.3 (0.7–2.0)	1.7 (0.5–2.4)	1.1 (0.5–2.3)	0.4 (0.2–0.9)
Suxamethonium	1.0 (0.5–1.7)	1.4 (0.5–2.4)	1.4 (0.5–2.3)	0.4 (0.2–0.9)
Gallamine	0.5* (0.2–1.6)	0.8 (0.5–1.2)	0.6 (0.3–1.3)	0.3 (0.1–0.6)
Pancuronium	0.9 (0.5–1.4)	0.5* (0.2–0.9)	0.5* (0.2–1.2)	0.4 (0.1–0.6)

Plasma potassium concentrations were compared by the analysis of variance.

RESULTS

In the 60 patients studied, there was no correlation between the fasciculation score and postoperative muscle pain at 24 h (fig. 1), 48 h or 72 h. Some patients had a high fasciculation score and a low myalgia score; others had a low fasciculation score and a high myalgia score. Pretreatment with suxamethonium had no significant effect on the fasciculation score or the myalgia score at 24, 48 or 72 h (table I). In contrast, gallamine significantly decreased the fasciculation score when compared with pretreatment with saline (from a median value of 1.3, to 0.5). Although postoperative myalgia scores were also decreased at 24, 48 and 72 h, these differences were not statistically significant. Pancuronium also decreased the fasciculation score, but to a lesser extent than gallamine (table I); nevertheless, it had a more marked effect on myalgia, and the decrease in postoperative muscle pain at 24 and 48 h was statistically significant (table I).

Moderately difficult or difficult intubation was commoner after pretreatment with gallamine or pancuronium (table II). Plasma potassium concentrations were not significantly affected by any of the pretreatments (table III). Saline and suxamethonium produced no change in concentration, while gallamine and pancuronium caused a slight decrease in plasma potassium concentrations.

TABLE II. *Effects of pretreatment with saline, suxamethonium, gallamine or pancuronium on intubation conditions after suxamethonium. Values represent the number of patients in each group*

	Assessment of ease of intubation		
Drug	Easy	Moderately difficult	Difficult
Saline	13	1	1
Suxamethonium	13	2	0
Gallamine	10	2	3
Pancuronium	12	1	2

DISCUSSION

This study was designed as a double-blind controlled trial of the effects of pretreatment with suxamethonium, gallamine or pancuronium on suxamethonium-induced fasciculations and postoperative myalgia. In practice, this aim was not entirely realized. As reported by previous authors [5, 6, 9, 10], a variable proportion of patients develop fasciculations after pretreatment ("self-taming") with suxamethonium. In the present study, this phenomenon was observed in two patients; it was not considered to invalidate the results of the investigation.

In this study, there was a delay of 45 s between pretreatment and the subsequent administration of suxamethonium. This latent period was shorter than the time interval in most other studies involving pretreatment with non-depolarizing neuromuscular blockers. Although many previous studies have used a latency of 1–3 min, there is no unequivocal evidence that this delay is required. Our previous studies suggested that both gallamine and pancuronium usually produce 50% neuromuscular blockade within 2 min [4]. Since suxamethonium itself requires approximately 1 min to produce comparable effects, it was considered that an interval of 45 s between pretreatment and the administration of suxamethonium was adequate.

Muscle fasciculations did not correlate significantly with postoperative myalgia at 24, 48 or 72 h. Some patients had marked fasciculations and no subsequent muscle pain, while others had no fasciculations, but developed severe myalgia. These results are generally consistent with previous studies [9, 11–13].

TABLE III. *Effects of pretreatment with saline, suxamethonium, gallamine or pancuronium on plasma potassium concentrations. Values represent means (SEM). The data were compared by the analysis of variance*

	Plasma potassium (mmol litre^{-1})	
Drug	Before induction	After induction
Saline	4.0 (0.1)	4.0 (0.1)
Suxamethonium	4.0 (0.1)	4.0 (0.1)
Gallamine	4.0 (0.1)	3.8 (0.1)
Pancuronium	4.1 (0.1)	3.9 (0.1)

Pretreatment with suxamethonium had no significant effect on muscle fasciculations; we were unable to confirm that their incidence was decreased, as reported by other authors [5, 9]. Similarly, postoperative myalgia at 24, 48 and 72 h was not decreased when compared with control subjects [9, 10].

It is generally accepted that gallamine and pancuronium decrease both muscle fasciculations and postoperative myalgia [11, 14, 15]. Nevertheless, in this study the two non-depolarizing neuromuscular blocking drugs appeared to have differential effects on these phenomena. Gallamine had a more marked effect on fasciculations than pancuronium, and the decrease in the fasciculation score was statistically significant. In contrast, pancuronium had a greater effect on myalgia, and significantly decreased postoperative muscle pain at 24 and 48 h. Other authors have suggested that gallamine is more effective than pancuronium in preventing muscle fasciculations [14, 16]. We propose that these differences may reflect the differential activity of gallamine and pancuronium at the neuromuscular junction. Gallamine may preferentially affect fasciculations by preventing prejunctional depolarization and local axon reflexes, and thus decrease the rate of motor unit firing. In contrast, the predominantly postsynaptic effects of pancuronium may mainly modify postoperative myalgia. In the U.K., gallamine is commonly used for pretreatment, since it is miscible with thiopentone and has a short duration of action; our results suggest that, although it may effectively prevent fasciculations (and by corollary, muscle movement during intubation), it is less effective than pancuronium in the suppression of postoperative myalgia.

In this study, moderately difficult or difficult intubation was commoner after pretreatment with gallamine or pancuronium, as anticipated from the results of other authors [16, 17]. Pretreatment with saline and "self-taming" had no effect on serum potassium concentrations immediately after administration of suxamethonium. The absence of hyperkalaemia may reflect the timing of the post-induction sample [17, 18]; however, in patients with peripheral denervation or burns, the maximal increase in serum potassium concentration occurs at 4–5 min [19, 20]. As shown in other studies, pretreatment with non-depolarizing myoneural blockers causes a slight decrease in plasma potassium concentrations within 5 min of the administration of suxamethonium [17].

In conclusion, this study suggests that non-depolarizing neuromuscular blocking agents with mainly presynaptic or postsynaptic effects may have differential effects on suxamethonium-induced fasciculations and myalgia. The development of blocking drugs with selective presynaptic and postsynaptic actions on neuromuscular transmission may well have different effects on these phenomena.

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EFFECT OF SURGICAL STIMULATION ON THE AUDITORY EVOKED RESPONSE

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SUMMARY

Previous studies have shown a dose-related effect of a number of general anaesthetic agents on the early cortical waves in the auditory evoked response (AER). In this study the effect of surgical stimulation on these waves was examined in 11 patients anaesthetized with thiopentone, nitrous oxide and halothane and paralysed with pancuronium. The inspired nitrous oxide concentration and end-tidal halothane concentration were held constant at 70% and 0.3%, respectively, and baseline AER recordings were made. Following surgical stimulation there was a progressive and significant increase in the amplitude of waves Nb and Pb/Pc. Unambiguous autonomic responses were seen in three patients, but these were not significantly correlated with changes in the AER. We conclude from this, and previous studies, that the amplitude of cortical waves in the AER are sensitive not only to anaesthetic concentration but also to surgical stimulation. The AER may, therefore, provide a useful index of depth of anaesthesia, that is the balance between the effects of surgical stimulation and anaesthetic depression on central nervous system activity.

At present there is no objective method of measuring "depth of anaesthesia" in routine clinical use. Approaches based on clinical signs such as changes in arterial pressure, heart rate and the size of the pupil are of limited value [1]. Consequently, anaesthetists rely on their experience to predict which dose of anaesthetic will provide the required anaesthesia. The numbers of patients reported to be awake but paralysed during anaesthesia, particularly for Caesarean section [2] reflect the shortcomings of this method.

To remedy this problem the anaesthetist should be provided with a signal which is not influenced by neuromuscular blocking drugs, shows graded responses with changing anaesthetic concentrations, behaves in the same fashion with all general anaesthetics, and reflects the activity of the central nervous system (CNS). Various electroencephalographic techniques have been used for monitoring brain function during anaesthesia [3, 4]. However, although these techniques have shown changes with increasing anaesthetic concentrations, a measurement has yet to emerge that changes in the same way with all general anaesthetics. In a series of investigations we [5–10] and others [11] have evaluated the usefulness of changes in the electroencephalogram (EEG) in response to an auditory click stimulus, as an index of depth of anaesthesia. This auditory evoked response (AER) may be subdivided into the brainstem response, which is obtained in the first 15 ms after stimulation, the early cortical response (from 15 to 80 ms) and the late cortical response (from 80 to 1000 ms). All of the anaesthetics that we have studied (halothane, enflurane, isoflurane, Althesin, etomidate and propofol) produced dose-related changes in the early cortical part of the response.

All of these data were obtained in patients anaesthetized before surgery; that is, patients who were undisturbed by extraneous stimuli other than the auditory clicks. However, the concept of "depth of anaesthesia" implies a state of the central nervous system resulting from a balance

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between the depression caused by anaesthetic drugs and arousal caused by surgical or other stimuli. An important requirement for a technique measuring depth of anaesthesia is that it reflects this balance. Thus if the AER remained unchanged when the anaesthetized patient was suddenly subjected to a surgical stimulus, the AER would be interpreted as a measure of anaesthetic concentration, but not of CNS activity. This study was designed to determine if the AER—obtained in an undisturbed patient during light steady-state anaesthesia—would show arousal in association with surgical stimulation.

PATIENTS AND METHODS

Patients and anaesthesia

Eleven female patients aged between 26 and 50 yr were investigated. Each patient had given informed consent to a study, the design of which was approved by the Northwick Park Hospital Ethics Committee. The patients were admitted for the operations listed in table I. Morphine 10 mg and atropine 0.6 mg were used as preoperative medication and anaesthesia was induced with thiopentone 2–4 mg kg^{-1}. The trachea was intubated following pancuronium 0.1 mg kg^{-1} and the lungs ventilated with 70% nitrous oxide in oxygen. The ventilation was adjusted to maintain an end-tidal carbon dioxide tension in the range 4.5–5.5 kPa (Hewlett–Packard capnograph 42710A). After the induction of anaesthesia, halothane was added to the inspired mixture and adjusted to maintain a constant end-tidal concentration of 0.3% (BOC Medishield mass spectrometer). Oesophageal temperature was measured with a thermistor positioned in the oesophagus at the level of the aortic arch. Arterial pressure and heart rate were recorded automatically at 5-min intervals (Dinamap: 843XT, Critikon).

The AER was measured using the technique previously described [5]. Click stimuli of intensity 75 dB above the average hearing threshold and 0.5 ms duration were applied at a rate of 6 s^{-1} to both ears. The EEG and click stimuli were recorded onto an FM tape recorder (Racal 4). Silver–silver chloride disc electrodes were used. The electrode sites chosen were mastoid referred to vertex and inion referred to vertex.

The EEG signals were subsequently analysed using a DATALAB DL 4000 averager. The averaged AER over the 130-ms post-stimulus interval was derived from 2048 stimulus presentations (taking 5–7 min unless there was electrical interference from the theatre equipment, in which case it could take longer). The AER was recorded continuously during a 45-min baseline period with steady-state anaesthesia before surgery. The AER was not sampled when minor procedures (e.g. bladder catheterization) were taking place. After the surgical procedure began the AER recordings were continued for a further 25 min. Particular care was taken to maintain constant end-tidal halothane concentrations. Values for the latencies of waves III and V and the amplitudes and latencies of Pa, Nb and the next positive wave, which we have labelled Pb/Pc (see Discussion), were derived from each averaged AER. In order to evaluate the autonomic response to surgery, note was made of pupillary dilatation, lachrymation, sweating, tachycardia and arterial hypertension: these were graded as shown in table II.

TABLE I. *The age and operations of the patients (all female) who took part in the study*

Patient	Age (yr)	Operation
1	41	Total abdominal hysterectomy
2	36	Bilateral stripping of varicose veins
3	38	Total abdominal hysterectomy
4	26	L. ankle triple arthrodesis
5	34	R. big toe arthrodesis
6	44	Total abdominal hysterectomy
7	36	Total abdominal hysterectomy
8	50	Total abdominal hysterectomy
9	37	Tubal surgery
10	47	Total abdominal hysterectomy
11	35	Total abdominal hysterectomy

TABLE II. *The gradation of autonomic responses of the 11 patients who took part in the study. Pupillary dilatation: + + + = sustained for longer than 1 h; + + = for longer than 10 min; + = some evidence; − = no evidence. Mean increase in arterial pressure: + + + = in excess of 20 mm Hg; + + = in excess of 10 mm Hg; + = increase 0–10 mm Hg; − = no change or a decrease. Mean increase in heart rate: + + = in excess of 10 beat min*$^{-1}$*; + = some increase; − = no change or a decrease. Sweating: + = evidence; − = no evidence. Tears: + = some evidence; − = no evidence. Anaesthetist's view: + + = unambiguous; + = equivocal autonomic response to surgery; − = no response*

Patient	Pupillary dilatation	Arterial pressure (mean inc.)	Heart rate (mean inc.)	Sweating	Tears	Overall anaesthetist's view
1	+	−	−	−	−	−
2	−	−	−	−	−	−
3	−	+ +	−	−	−	−
4	+ +	+ + +	+ +	−	−	+ +
5	−	−	−	−	−	−
6	+ + +	+ +	−	−	−	+ +
7	+	+ +	−	−	+	+
8	+	+	−	−	−	+
9	−	+ +	−	−	−	−
10	+ + +	+ +	−	−	+	+ +
11	+	−	−	−	−	−

Statistical analysis

Analysis of variance was carried out on each variable measured from the AER. Data from the 24 min before and the 24 min after the incision were used. These data (before and after incision) were each divided into two 12-min periods.

First, we compared the data before and after incision and then we compared the difference between the two periods before incision with the difference between the two periods after incision; that is, we tested for a significant surgery × period interaction. In this analysis the data before incision are used as a baseline to indicate the kind of changes that would be expected from two consecutive 12-min periods. Finally, we tested whether the effects of surgery were related to the autonomic "responder" or "non-responder" classification; that is, we tested for a significant surgery × responder interaction.

RESULTS

Description of data

Changes in the AER with surgery. The averaged early cortical responses of an anaesthetized patient before and after surgical incision are shown in figure 1. The most striking changes were in the amplitudes of Pa, Nb and Pb/Pc which were larger during surgery than before, resembling what would be expected from a lower end-tidal concentration of volatile anaesthetic—despite the end-tidal halothane concentration being maintained constant throughout. Not all patients showed these increases following incision. Pa increased following surgery in six of 11 patients, Nb increased in eight of 11 patients and Pb/Pc in nine of 11 patients. The Nb and Pb/Pc data for individual patients are plotted in figure 2.

Autonomic responders v. *non-responders.* Of the 11 patients, only three showed a clear response to

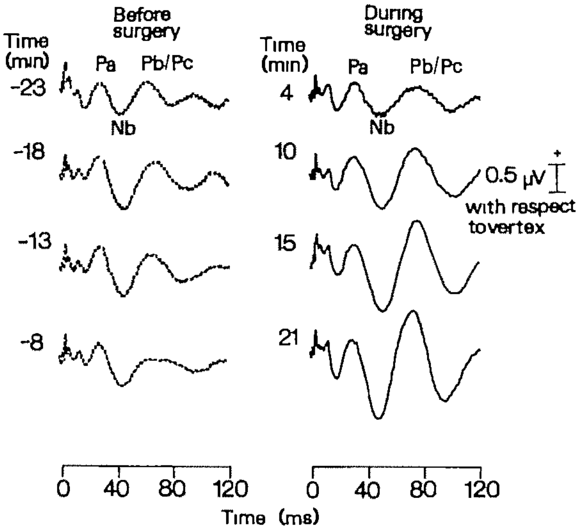

FIG. 1. The early cortical responses of one patient. In the left-hand panel are the traces before surgery and in the right-hand panel are those during surgery, starting from first incision. Each average took approximately 6 min to collect; the times given correspond to the middle of that period.

surgery as judged by autonomic signs. Data from these patients are shown on the left in figure 2. All three patients showed increases in the amplitudes of Nb and Pb/Pc. It was the possibility of a relationship between the autonomic changes and those seen in the AER that prompted us to include the "responder" and "non-responder" classification in the analysis of variance model.

Table II summarizes the changes in the autonomic responses on which this classification was

TABLE III. *Effect of surgery on the latencies and amplitudes of the brainstem and early cortical waves. Mean difference (during – before), SEM and significance of difference of data obtained before and during surgery. Mean values obtained during each 12-min period before and during surgery, together with significance of the surgery × period interaction.* P > *0.05 = ns*

	Mean change following surgery			Means for each period				
				Before incision (min)		After incision (min)		
	Mean diff.	SEM	*P*	24–12	12–0	0–12	12–24	*P*
Latency (ms)								
I	0.01	0.019	ns	1.87	1.87	1.89	1.88	ns
III	0.02	0.017	ns	4.12	4.11	4.14	4.14	ns
V	0.07	0.016	< 0.01	6.15	6.18	6.23	6.24	ns
III–V	0.04	0.015	< 0.05	2.03	2.07	2.09	2.10	ns
Pa	0.90	0.72	ns	34.2	34.4	35.1	35.4	ns
Nb	2.1	1.60	ns	51.5	53.1	53.9	55.0	ns
Pb/Pc	3.6	2.10	ns	72.4	73.8	77.0	76.5	ns
Amplitude (μV)								
Pa	0.04	0.068	ns	0.52	0.44	0.48	0.56	ns
Nb	0.20	0.088	< 0.05	0.39	0.35	0.48	0.66	< 0.01
Pb/Pc	0.22	0.082	< 0.01	0.22	0.24	0.34	0.57	< 0.01

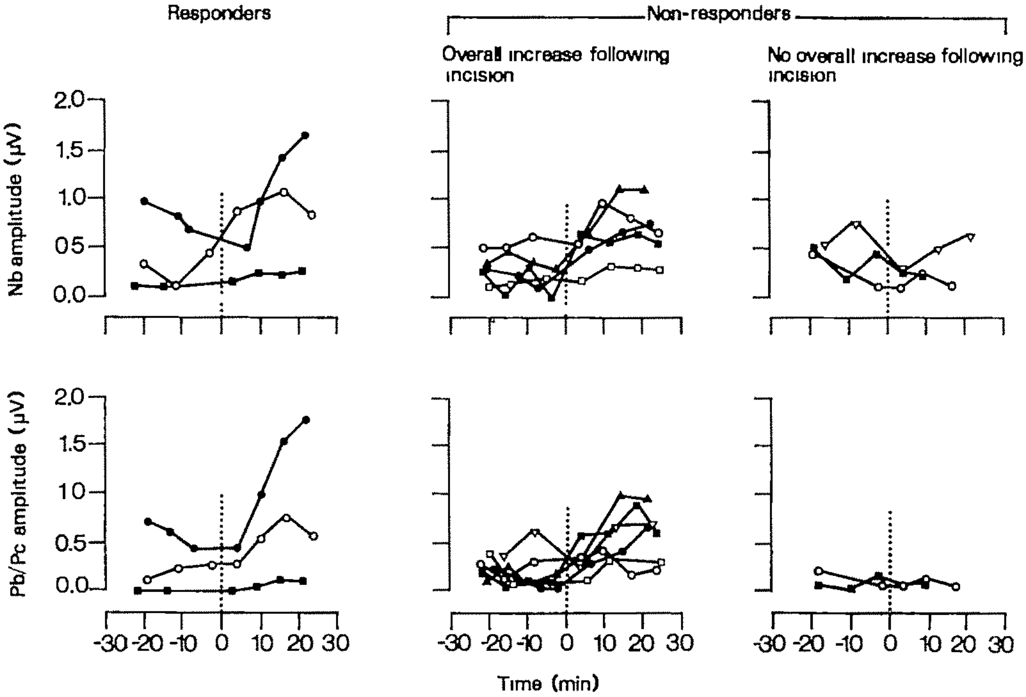

FIG. 2. Nb and Pb/Pc amplitudes against time (min) for individual patients. Incision is indicated by a vertical dotted line.

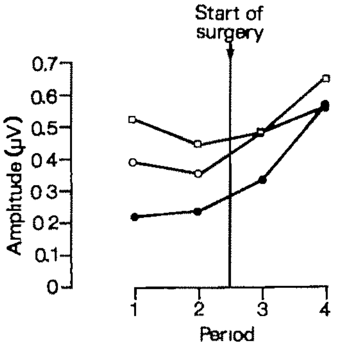

FIG. 3. The means for the 11 subjects of Pa (□), Nb (○) and Pb/Pc (●) amplitude for the periods 1 (24–12 min) and 2 (12–0 min) before incision, and periods 3 (0–12 min) and 4 (12–24 min) after incision.

based, along with the anaesthetist's overall impression at the time. The three patients who were classed as unambiguous responders had high scores for pupillary dilatation and for the mean increase in arterial pressure. None of the patients showed sufficient change in autonomic function to prompt the anaesthetist to administer more general anaesthetic agent and no patient reported awareness of the surgical procedure, hearing voices or unusual dreams.

Statistical analyses

Effect of surgery. There were significant increases in the amplitudes of waves Nb and Pb/Pc and increases in the latency of wave V and the III–V interval following surgical incision. The mean changes following incision are given in table III. The mean values for each period are also presented in table III and are plotted for Pa, Nb and Pb/Pc amplitudes in figure 3. Only the amplitudes of Nb and Pb/Pc showed significant surgery × period interactions. During surgery these values were increased during the second period compared with the first, whereas before surgery there was essentially no difference between the two periods.

Relationship to "responder" status. None of the variables tested showed a significant surgery × responder interaction; that is, responders and non-responders were not different with respect to the effect of surgery on the AER.

DISCUSSION

Before the start of surgery, at a constant end-tidal concentration of anaesthetic, the appearance of the AER was similar to previously published data with the same anaesthetic (compare the left-hand panel of figure 1 with figure 4).

Surgical stimulation partially reversed the changes in the early cortical waves brought about by halothane anaesthesia in that, before surgery (fig. 1) the AER was, in appearance, midway between the 0.12% and 0.66% end-tidal halothane traces seen in figure 4, whereas during surgery it was more similar to the 0.12% halothane trace. Increases in amplitude of waves Nb and Pb/Pc acounted for the changes in appearance. Most, although not all, patients showed these changes. This variability in response is perhaps not surprising in view of the variability in the sensitivity of individual patients to anaesthetics and surgical stimulation.

Our labelling of the positive peak following Pa possibly warrants explanation. The characteristic features of the middle latency components of the AER following induction of anaesthesia breathing 70% nitrous oxide in oxygen are *three* positive waves, Pa, Pb and Pc. With the addition of

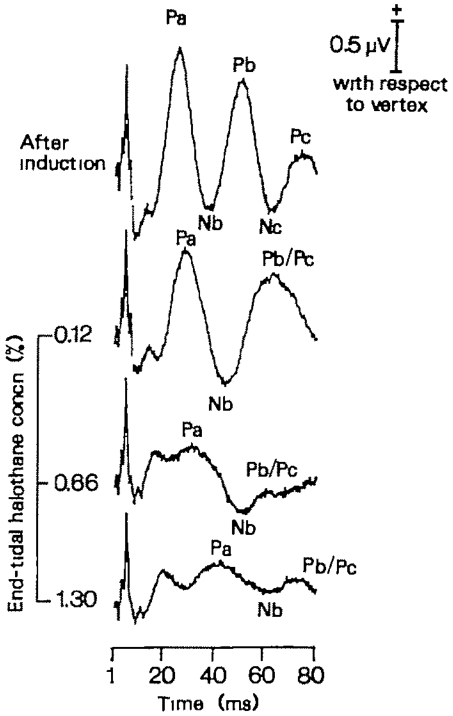

FIG. 4. The changes in the early cortical response with halothane anaesthesia; the averaged AER for one patient following the induction of anaesthesia and at the halothane concentrations given. (Reproduced after Thornton and colleagues [6], with permission.)

halothane sufficient to give an end-tidal concentration of 0.12%, only two positive waves are normally seen. There is no certainty whether Pb and Pc have combined or whether one or the other has disappeared. Because of this uncertainty, the positive wave following Pa has been labelled Pb/Pc.

The amplitudes of Nb and Pb/Pc were significantly increased during surgery compared with before surgery. To counter the argument that these were progressive time-related changes and not the result of surgery *per se*, we examined the surgery × period interaction. In this analysis we compared the trend before surgery with the trend following surgery. These trends were derived from the difference between two consecutive 12-min periods, this duration being chosen to include two data points from each patient. Following surgery there was a statistically significant change in the trend. The increase during surgery in the amplitude of Nb an Pb/Pc could not, therefore, be explained by a time trend occurring throughout the study and has to be attributed specifically to surgical stimulation. Further, this effect was more pronounced in the 12–24 min following incision than in the preceding 12 min. Possibly, following incision, the degree of stimulation increased as surgery progressed.

In contrast to the effect on wave amplitude, surgical stimulation did not reverse the effect of halothane on wave latencies (halothane increases the latencies). Following incision there were small increases in latency for all waves compared with pre-incision values, but only the changes in V latency and III–V interpeak interval were significant and none showed a significant surgery × period interaction. As these changes were progressive throughout the study they cannot be attributed to surgical stimulation and were possibly the result of gradually increasing anaesthetic concentration in the brain in spite of constant end-tidal halothane. The latency of the brainstem [3] and early cortical waves [12] have been shown to depend on temperature, but there were no changes in temperature in our patients which could account for these changes in amplitude or latency.

The amplitudes of the early cortical response, but not the latencies, show promise as measures of depth of anaesthesia. This fits with the results of a previous study [10] in which, in contrast to changes in amplitude, the changes in latency brought about by three inhalation agents (halothane, enflurane and isoflurane) did not correspond to their anaesthetic potency as determined by MAC.

The effects of surgery on the AER in the three patients that were classified "responders" were not significantly different from those occurring in the eight that were considered "non- or equivocal responders". However, there is little statistical power for this comparison. A lack of association between the broad classification responder–non-responder and an overall change in the AER with surgery does not preclude an association between transient cardiovascular and AER changes. There is scope for further examination of the relationship between autonomic and AER variables when it is possible to obtain reliable data for shorter periods of time.

Reversal of the depressant effect of anaesthetics on the evoked response has been reported previously. Angel and colleagues [13] showed that the amplitude of the cortical parts of the somatosensory response in rats decreased with increasing anaesthetic concentration. These changes were reversed when ambient pressure was increased. Increasing the ambient pressure also increased the dose of anaesthetic required to prevent reflex response to tail stimulation. Other workers have shown that various stimuli may reverse the effects of anaesthesia on the EEG. For example, surgical stimulation of patients anaesthetized with halothane produced an arousal pattern in the EEG; that is, a reduction in amplitude and an increase in frequency [14]. Therefore, it seems reasonable to suppose that increases in the amplitudes of the early cortical AER with surgery, which we report here, also represent arousal of the CNS. Erwin and Buchwald [15] found that the cortical waves in the AER (latencies 55–80 ms) decreased in amplitude during slow wave sleep and recovered to the pattern seen in wakefulness during rapid eye movement sleep, suggesting that waves at these latencies provide a unique probe of tonic brain activity. Picton and Hillyard [16] demonstrated an increase in amplitude of the early cortical wave (N1) (83-ms latency) in conscious man when attention was aroused by specific, transient changes in auditory signal.

In conclusion, the amplitudes of the early cortical waves show graded changes with anaesthetic drug concentrations and the changes are similar for at least six general anaesthetic drugs [5–10]. We have demonstrated in this study that these changes are not dependent upon anaesthetic concentration alone since, at a constant anaesthetic concentration, they may be partially reversed by surgical stimulation. The amplitudes of the early cortical response, in particular of the waves Nb and Pb/Pc, seem worthy of further investigation as they reflect the balance between the depression of the CNS by general anaesthetics and its stimulation by surgery, that is the "depth of anaesthesia"

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INTRAOCULAR PRESSURE CHANGES DURING RAPID SEQUENCE INDUCTION OF ANAESTHESIA: COMPARISON OF PROPOFOL AND THIOPENTONE IN COMBINATION WITH VECURONIUM

R. K. MIRAKHUR, W. F. I. SHEPHERD AND P. ELLIOTT

SUMMARY

Intraocular pressure (IOP) was measured during rapid sequence induction of anaesthesia using thiopentone or propofol as the induction agent and vecuronium for neuromuscular blockade. Vecuronium was administered in a dose of 0.15 mg kg^{-1} approximately 35 s before the induction agent. IOP was measured with a hand-held applanation tonometer before anaesthesia, following administration of the induction agent, immediately after tracheal intubation and cuff inflation and 1, 2 and 3 min later. IOP in the propofol group was significantly lower than in the thiopentone group, except immediately after induction, when reduction in IOP was similar and significant with both agents. IOP following intubation in patients in whom anaesthesia was induced with thiopentone was not significantly different from baseline values, but showed a significant increase from the pressure before intubation. In contrast, IOP after intubation in the propofol group remained not only significantly less than the baseline value, but also showed only a minimal and insignificant change in comparison with values before intubation. The frequency of side effects was low in both groups except for a significantly greater reduction in arterial pressure in those receiving propofol.

Induction of anaesthesia with propofol (2,6,-diisopropylphenol) has been reported to be smooth, without major adverse effects and associated with rapid, smooth recovery [1–3]. Previous studies have shown that its use is also associated with significant reduction in intraocular pressure (IOP) and some benefit in attenuating the increase in IOP associated with tracheal intubation. In addition, many of these patients may present with a full stomach, but the use of perforated eye injuries. This is particularly so during induction of anaesthesia and tracheal intubation. In addition, many of these patients may present with a full stomach, but the use of suxamethonium (which is the neuromuscular blocking agent of choice for a rapid sequence induction in patients with a full stomach) may be considered contraindicated in patients with perforated eye injuries because of its well documented effect in increasing IOP. In the present study, intraocular pressure changes have been studied during a rapid sequence induction using propofol or thiopentone in combination with vecuronium.

PATIENTS AND METHODS

Forty adult patients conforming to ASA grades I or II were included in the study after their informed consent and approval from the Regional Ethics Committee had been obtained. All were to undergo elective ophthalmic surgery and any patient with an increased IOP (more than 20 mm Hg) before operation was excluded from the study. Premedication consisted of diazepam 10–15 mg by mouth. On arrival in the anaesthetic room the patient was given fentanyl 2 µg kg^{-1} i.v. Preoxygenation was carried out for 5 min with the face mask being held lightly by the patient. Vecuronium was administered in a dose of 0.15 mg kg^{-1}. This was followed, as soon as the earliest subjective feelings of muscle weakness such as the

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TABLE I. *Grading of intubating conditions*

Grade	Criteria
Excellent	Good jaw relaxation, vocal cords open, no response to intubation
Satisfactory	Good jaw relaxation, vocal cords open, minimal reaction to intubation
Fair	Jaw relaxed, cords moving, intubation requiring firm pressure and accompanied by moderate bucking or coughing
Poor	Intubation impossible because of poor jaw or cord relaxation

TABLE II. *Intraocular pressure (mm Hg ± SD). Differences from baseline significant*: $^{*}P < 0.01$; $^{**}P < 0.001$. *Differences significant between propofol and thiopentone groups at all times except baseline and after induction*; $P < 0.05$–$P < 0.005$

	Propofol	Thiopentone
Baseline	14.4±2.46	14.1±2.75
After induction	9.1±3.09**	9.8±2.23**
After intubation	9.9±2.79**	13.0±3.77
1 min after intubation	6.6±3.05**	10.8±4.21*
2 min after intubation	5.9±2.48**	9.3±3.63**
3 min after intubation	5.7±2.58**	7.8±2.90**

heaviness of the eyelids appeared, by the rapid administration of propofol or thiopentone, in a dose sufficient to abolish verbal communication with the patient. Cricoid pressure was applied immediately after administration of the induction agent and intubation and cuff inflation carried out 30 s later. Ventilation was started at this stage with nitrous oxide and isoflurane in oxygen.

IOP was measured using a hand-held applanation tonometer before induction of anaesthesia (using amethocaine), after administration of the induction agent, immediately after intubation and cuff inflation and 1, 2 and 3 min later. Heart rate and systolic arterial pressure were measured at the same time as IOP using an electrocardiograph and oscillotonometer (Dinamap). The time to onset of complete blockade and duration of clinical neuromuscular blockade by vecuronium were determined using a peripheral nerve stimulator (Myotest) delivering a train-of-four stimulation at 2 Hz every 10 s via cutaneous electrodes. Onset of complete block was defined as the time from administration of the blocking drug to the disappearance of all four responses, and the duration of clinical blockade as the time from administration of the myoneural blocker to the reappearance of all the four responses. Further smaller increments of vecuronium were administered as required at this stage. Intubating conditions were graded on a four-point scale as excellent, satisfactory, fair or poor, according to criteria listed in table I. Residual neuromuscular blockade was antagonized at the end of surgery with a mixture of neostigmine and glycopyrrolate. Side effects such as pain on injection, hiccup or spontaneous movements were also recorded. Patients were questioned the next day about the acceptability of anaesthesia.

The results were tested for statistical significance by analysis of variance and *t* tests. Intubating conditions were compared using the Fisher's Exact Test.

RESULTS

The mean age and weight were 40 (16.4) yr (SD) and 66 (12.9) kg for the propofol group, and 43 (18.3) yr and 71 (12.7) kg for the thiopentone group, respectively, and these were not significantly different. The baseline IOP values were 14.4 (2.4) and 14.1 (2.75) mm Hg in the propofol and thiopentone groups, respectively; again the difference was not significant. IOP decreased significantly ($P < 0.001$) following administration of both propofol and thiopentone (table II). The reduction was greater with propofol (5.3 mm Hg or 37%) than with thiopentone (4.3 mm Hg or 30%), but this difference between the groups was not statistically significant. The IOP after intubation and cuff inflation increased from 9.8 mm Hg to 13.0 mm Hg in the group in whom anaesthesia was induced with thiopentone. Although it was still less than the baseline value, the increase from the value just before intubation was significant ($P < 0.01$). The IOP in the group given propofol increased from 9.1 to only 9.9 mm Hg following intubation and this change was not statistically significant. IOP was significantly less than ($P < 0.01$) the baseline values in both groups for the remainder of the study period. IOP values in the propofol group were significantly lower ($P < 0.05$) than in the thiopentone group throughout the study period, with the exception of the value recorded immediately after induction.

Mean systolic arterial pressures (table III) before induction of anaesthesia were not sig-

TABLE III. *Systolic arterial pressure (mm Hg ± SD). Differences significant compared with baseline*: *$P < 0.05$; **$P < 0.005$. *Differences significant between propofol and thiopentone groups throughout except baseline* ($P < 0.005$)

	Propofol	Thiopentone
Baseline	139 ± 14.5	151 ± 24.6
After induction	125 ± 18.7**	154 ± 29.2
After intubation	129 ± 27.2	163 ± 30.3*
1 min after intubation	115 ± 21.4**	158 ± 33.1
2 min after intubation	108 ± 21.6**	148 ± 29.9
3 min after intubation	104 ± 21.3**	141 ± 28.8*

TABLE V. *Intubating conditions and neuromuscular blockade*

	Propofol ($n = 20$)	Thiopentone ($n = 20$)
Intubating conditions		
Excellent	17	13
Satisfactory	3	7
Time (± SD) to onset of complete blockade (s)	210 ± 62.4	187 ± 36.7
Duration (± SD) of clinical blockade (min)	42 ± 8.5	44 ± 6.7

TABLE IV. *Heart rate (beat min^{-1} ± SD). Differences from baseline significant*: *$P < 0.05$; **$P < 0.005$. *Differences significant between propofol and thiopentone throughout* ($P < 0.01$) *except baseline*

	Propofol	Thiopentone
Baseline	82 ± 21.3	77 ± 17.3
After induction	85 ± 16.7	97 ± 19.1**
After intubation	88 ± 16.6	105 ± 16.4**
1 min after intubation	85 ± 16.1	100 ± 16.4**
2 min after intubation	83 ± 16.0	93 ± 15.7**
3 min after intubation	80 ± 16.7	88 ± 14.6*

nificantly different in the two groups. Arterial pressure decreased significantly ($P < 0.005$) in the propofol group and remained so throughout the study period except after intubation. In the thiopentone group the only significant changes in arterial pressure were an increase after intubation ($P < 0.01$) and a decrease 3 min later ($P < 0.05$). The average peak decrease in systolic arterial pressure was 25.4 % in the propofol group and 7.1 % in the thiopentone group. Eleven patients receiving propofol demonstrated a decrease in arterial pressure of greater than 25 %, three of these exhibiting a reduction of more than 40 %. However, hypotension was transient and responded to 500–1000 ml of crystalloid solutions.

Heart rate responses in the two groups were also different (table IV). There was no significant change in mean heart rate in those given propofol, but heart rate increased significantly in those given thiopentone ($P < 0.01$) with a peak increase of approximately 37 % after intubation.

The average time between administration of vecuronium and induction agent was approximately 35 s. The intubating conditions and the onset and duration of clinical neuromuscular blockade are shown in table V. All the intubations were graded as satisfactory, but more were graded as excellent in those receiving propofol (17 compared with 13). The onset and duration of clinical blockade of the initial 0.15-mg kg^{-1} dose of vecuronium were 187 and 210 s and 42 and 44 min, respectively, in propofol and thiopentone groups (ns).

The average induction doses of propofol and thiopentone were 2.5 and 5.4 mg kg^{-1}, respectively, and the majority of injections were made to a vein on the dorsum of the hand. End-tidal carbon dioxide concentration during surgery was maintained between 3.5 and 4.0 %. One patient in each group complained of mild discomfort on administration of the induction agent. There were no other side effects. Four patients in the propofol group and six in the thiopentone group suffered from nausea, vomiting or both in the immediate postoperative period. There was no venous sequelae 24 h after anaesthesia. The induction sequence was deemed acceptable by all patients when they were questioned the day after anaesthesia.

DISCUSSION

Induction of anaesthesia for repair of a perforated eye injury in a patient with a full stomach is a challenging situation for the anaesthetist. The important considerations are the protection of the airway from the hazard of regurgitation and aspiration of the gastric contents, and preventing increases in IOP, consequent upon tracheal intubation, with the harmful possibility of further damage to the eye and even loss of the intraocular contents. The role of neuromuscular blocking agents has been the subject of many previous investigations, but in the present study the choice of the induction agent and the induction sequence itself have been examined.

Suxamethonium is considered the myoneural blocker of choice for facilitating tracheal intubation during a rapid sequence induction in patients with a full stomach. However, its use is associated with an increase in IOP [6–8]. Vecuronium was used in the present study both for its beneficial effect in terms of a significant reduction in IOP [9, 10] and for its relatively short duration of action and lack of side effects, even when used in a moderately large dose of 0.15 mg kg^{-1} [11].

It is well known that tracheal intubation itself may produce an increase in IOP irrespective of the neuromuscular blocking agent used [6, 8, 12, 13]. On this basis and because they could find no evidence of extrusion of ocular contents from retrospective analysis of case records, Libonati, Leahy and Ellison [14] advocated that it was safe to use suxamethonium in patients with perforated eye injuries, and this view has been supported in a more recent review [15]. However, Libonati, Leahy and Ellison [14] reviewed the records of fewer than 50% of the patients admitted with such eye injuries. In addition, they did not comment on the visual function of these patients and they could not have known if avoiding suxamethonium would have resulted in better functional results.

It has been shown that, although the IOP increases following intubation with the use of both depolarizing and non-depolarizing neuromuscular blockers, the change is less with the use of the latter [8]. Non-depolarizing blocking agents such as pancuronium or alcuronium have been recommended for rapid sequence induction in patients with perforated eye injuries [16, 17], this suggestion being based on the fact that, in these studies, IOP after intubation was not significantly higher than the baseline values, even though the IOP increased following intubation.

The technique of induction, in addition to the induction agent itself, has received little attention in rapid sequence inductions, regarding effects on IOP. Thiopentone is known to produce a significant reduction in IOP [13, 18]. Recent studies have not only confirmed this, but also shown that the newer agent, propofol, produces an even greater reduction in IOP and that its use may attenuate the subsequent increase in IOP produced by intubation [4, 5]. It appears that this advantage of propofol is also apparent when it is used as part of a rapid sequence induction. This benefical effect of propofol may be the result of significantly greater hypotension with its use [2, 4, 5, 19], lack of antanalgesic action [20] or a possible greater "depth of anaesthesia" [21]. The doses of propofol and thiopentone required to induce anaesthesia in the present study are similar to those reported by others during normal induction in adult patients [2, 22].

The technique of induction has been shown to have important effects on IOP. Where an induction agent such as thiopentone is administered in a conventional manner before large doses of atracurium or vecuronium, there is still an increase in IOP following intubation [23]. This also occurs when propofol is the induction agent [24]. In the present study the administration of the induction agents after vecuronium ensured that the intubation was carried out at the peak effect of the induction agent and also approximately 90 s after administration of vecuronium (approximately 35 s between administration of the neuromuscular blocker and the induction agents, 25–30 s for administering the induction agent, and intubation 30 s after their administration). It has been shown previously that intubating conditions with vecuronium in doses of 0.1–0.15 mg kg^{-1} are satisfactory at approximately 90 s and that intubation using these doses can be carried out in the absence of complete paralysis [11, 25]. As a result of the use of propofol, vecuronium and this induction sequence, intubation was associated with only a small, insignificant increase in IOP.

Careful assessment of the airway should be made before administration of the neuromuscular blocker, as would be the practice in any other situation. In the event of anticipated difficulty in intubation, it is prudent to avoid the use of myoneural blockade, to starve the patient and to use other means of securing the airway.

Because of the significantly greater reduction in arterial pressure with the use of propofol, this agent should be used with caution or even avoided in situations in which severe hypotension is undesirable. However, the advantage of good control of IOP in otherwise healthy patients with perforated eye injuries may outweigh the risk of hypotension, which is usually transient and responds to simple measures such as i.v. fluid administration [5].

In conclusion, good control of IOP is achieved during a rapid sequence induction when vecuronium is followed by propofol. This may be a suitable technique for induction of anaesthesia in patients with a full stomach who are to undergo repair of perforated eye injuries, provided there are no contraindications to either the use of any of the agents used or the technique itself.

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MODIFICATION BY ALFENTANIL OF THE HAEMODYNAMIC RESPONSE TO TRACHEAL INTUBATION IN ELDERLY PATIENTS

A Dose–Response Study

I. J. KIRBY, D. NORTHWOOD AND M. E. DODSON

SUMMARY

Fifty-five elderly patients undergoing elective ophthalmological surgery were randomly allocated to four groups. Following the induction of anaesthesia with thiopentone (given over 2 min) and the administration of atracurium 0.6 mg kg^{-1}, patients received alfentanil 400, 600, 800 or 1000 µg. Intubation of the trachea was performed 90 s later. Heart rate was monitored continuously and systolic arterial pressure was measured at 1-min intervals for 3 min before induction, and both variables were monitored until 10 min had elapsed after tracheal intubation. In each of the groups there was a significant decrease in systolic arterial pressure and a significant increase in heart rate on induction of anaesthesia. In those patients who received either 400 or 600 µg of alfentanil, arterial pressure increased immediately after tracheal intubation, whereas in those receiving alfentanil 800 or 1000 µg, arterial pressure decreased immediately after tracheal intubation, and when measured 10 min after intubation. It is suggested that alfentanil 600 µg (10 µg kg^{-1}) constitutes the optimal dose with which to obtund the haemodynamic response to tracheal intubation in elderly patients, and to minimize cardiovascular depression after tracheal intubation.

Patients over the age of 70 yr form an important at-risk group in whom cardiovascular stability during tracheal intubation is desirable. Previous studies [1–4] have shown alfentanil to be effective in obtunding the haemodynamic response to tracheal intubation in younger adults. Doses used in these studies ranged from 15 to 30 µg/kg body weight. Little has been reported about the use of alfentanil in elderly patients. This study investigated the effects of this drug on the haemodynamic changes in response to laryngoscopy and intubation in patients older than 70 years of age.

PATIENTS AND METHODS

The investigation was conducted prospectively on 55 patients, all older than 70 yr, undergoing elective ophthalmological surgery. They were of ASA class I–III and all gave their informed consent to the study, which was approved by the local ethics committee.

The patients did not receive any sedative premedication, but were allowed to take any usual morning medication. However, those receiving β-adrenoceptor blocking drugs or calcium antagonists were excluded from the study.

Before entering the anaesthetic room, patients were allocated randomly to one of four groups (A, B, C, D) to receive alfentanil 400, 600, 800 or 1000 µg, respectively. A pilot study had previously been performed, which demonstrated 200 µg to be ineffective in preventing the pressor response to laryngoscopy, and this precluded the use of a control group.

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In the anaesthetic room, an infusion of 5% Dextrose in water was established using a 16-gauge 2-Y CAN, following infiltration of the skin with 1 ml of 1% lignocaine. ECG monitoring was commenced (Simonsen and Weel Diascope 2 monitor) and displayed continuously. This also gave a digital display of heart rate. Arterial pressure was recorded using a Dinamap 846 automatic arterial pressure monitor placed over the brachial artery. The readings were recorded with an automatic printer.

Once three consecutive readings of arterial pressure were similar (within 5 mmHg), anaesthesia was induced with thiopentone given slowly over a minimum period of 2 min, until loss of the eyelash reflex occurred. Following the induction of anaesthesia, patients received atracurium 0.6 mg kg^{-1} and, 90 s after the atracurium, each patient received the allocated dose of alfentanil. After a further 90 s tracheal intubation was performed. At the onset of apnoea patients received gentle manual ventilation via a Mapleson A breathing system and facemask. Fresh gas flows of oxygen 3 litre min^{-1} and nitrous oxide 6 litre min^{-1} were used throughout the procedure until 10 min had elapsed after tracheal intubation. Volatile inhalation agents were not used during the study.

End-tidal carbon dioxide concentration was monitored with a Datex capnograph, the tip of its sampling catheter being placed 1 cm proximal to the tip of a nasopharyngeal airway before intubation, and attached to a Portex connector after intubation. Artificial ventilation was instituted and adjusted to ensure normocarbia during the study. Heart rate was displayed continuously and systolic arterial pressure was measured every 1 min throughout the procedure until 10 min had elapsed since the intubation of the trachea.

The "pre-induction" values were calculated as the mean of the three similar values measured in the anaesthetic room. The "post-induction" values were measured 1 min after the administration of atracurium but before the alfentanil. The "post-intubation" values were the maximum recorded values during the first 5 min after tracheal intubation. The "final" values were measured 10 min after intubation. The variables recorded included systolic arterial pressure (SAP), and heart rate (HR).

Data were analysed using Student's *t* test, paired tests being used within groups and unpaired tests being used between groups.

RESULTS

There were no significant differences in mean age, weight and pre-induction cardiovascular variables between patients in each of the four groups (table I). Induction of anaesthesia was achieved with a mean dose of thiopentone 2.5 mg kg^{-1} (range 0.9–4.0 mg kg^{-1}). The trachea was intubated successfully in all patients.

Systolic arterial pressure

Systolic arterial pressure decreased by between 11.7 and 20.5 mm Hg in all groups following the induction of anaesthesia, but there was no significant difference between the groups (table II).

The pressor response to tracheal intubation was significantly attenuated in groups C and D when compared with group A, and in group C when compared with group B.

The final values of systolic arterial pressure were smaller in all groups when compared with pre-induction values. The decrease was significantly greater in group C when compared with groups A and B, and in group D when compared with group A.

Heart rate

Following tracheal intubation an increase in heart rate occurred in all groups; this varied from 10 to 26 beat min^{-1}. This was most marked in

TABLE I. *Number of patients in each group; dose of alfentanil and mean (SEM) age, weight, pre-induction heart rate and systolic arterial pressure in each group*

	Group A	Group B	Group C	Group D
Dose of alfentanil (μg)	400	600	800	1000
No. patients	14	15	13	13
Mean age (yr)	76.4 (0.9)	76.8 (1.6)	77.8 (1.4)	76.3 (0.7)
Mean weight (kg)	63.7 (5.1)	60.4 (3.2)	64.8 (3.1)	65.7 (2.9)
SAP (mm Hg)	160.6 (7.9)	156.8 (6.9)	161.5 (7.1)	169.5 (7.2)
HR (beat min^{-1})	74.1 (4.3)	75.3 (2.6)	71.6 (2.0)	71.3 (4.5)

TABLE II. *Changes (mean, SEM) in systolic arterial pressure (mm Hg) after induction of anaesthesia, after intubation and (final) 10 min after intubation. All values compared with pre-induction. Significant differences between groups in same column :* *P < 0.05 (C v. B, D v. A); **P < 0.01 (A v. C)

	After induction		After intubation		Final	
Group	Change	SEM	Change	SEM	Change	SEM
A	−11.7	4.0	+18.2**	7.0	−12.1**	5.9
B	−19.3	4.9	+9.4	7.8	−13.5	8.2
C	−14.5	7.6	−19.1*	6.5	−33.1*	7.6
D	−20.5	5.9	−17.9*	9.7	−31.4*	5.8

TABLE III. *Changes (mean, SEM) in heart rate (beat min^{-1}) after induction of anaesthesia, after intubation and (final) 10 min after intubation. All values compared with pre-induction. Significant differences between groups in this column :* *P < 0.05 (B v. A, C v. A) **P < 0.01 (D v. A)

	After induction		After intubation		Final	
Group	Change	SEM	Change	SEM	Change	SEM
A	+10.2	1.6	+26.0	2.9	+0.6	5.5
B	+7.7	2.6	+12.7*	5.0	−8.9	4.0
C	+12.5	2.5	+9.8*	3.6	−7.3	3.3
D	+7.5	2.7	+10.8**	2.6	−5.6	4.6

group A (table III), being significantly different from values in groups B, C and D.

Ten minutes after intubation the final heart rates were less than pre-induction values in groups B, C and D, but in group A the final heart rate was 0.6 beat min^{-1} greater than the pre-induction value. However, these differences were not statistically significant between the groups.

Heart rhythm was noted throughout the study. No serious cardiac arrhythmia occurred. Three patients developed unifocal ventricular ectopic beats during the post-intubation period (one in each of groups A, B and D). In each case the ectopic beats resolved spontaneously and did not require therapeutic intervention. Intubating conditions were good in all the patients studied. None of the patients developed ventilatory depression in the postoperative period.

DISCUSSION

Increases in heart rate and systolic arterial pressure can increase the workload of the heart and thus increase myocardial oxygen requirement. This is undesirable in the older patient, who is likely to have some pathophysiological changes in the coronary vessels and myocardium, which reduce the ability to meet the increased myocardial oxygen demand. Thus elderly patients are more susceptible to the development of myocardial ischaemia. Therefore, it is particularly valuable to be able to reduce, or prevent, the pressor response to tracheal intubation in this age group.

In this study a clear relationship has been shown between the dose of alfentanil and the effect of tracheal intubation on systemic arterial pressure. Only the 800- and 1000-µg doses prevented any increase in systolic arterial pressure at intubation, when compared with pre-induction values. The effect on heart rate was less clearly dose-related, although the use of the smallest dose (400 µg) was followed by a marked increase in heart rate at intubation which was not seen with the three larger doses.

Dose-related effects on the cardiovascular system were also recorded 10 min after intubation. At this time, systolic arterial pressure had decreased from its pre-induction values in all groups, and the lowest pressures were observed after the administration of the two largest doses of alfentanil. In these two groups (C and D) systolic arterial pressure was 31–33 mm Hg less than its pre-induction value. Changes in heart rate were again less clearly dose-related, but a decrease was seen after the three largest doses which was not seen after the smallest dose (table III).

The cardiovascular effects of tracheal intubation can be affected by other factors. The administration of thiopentone can cause a marked and immediate decrease in arterial pressure, and the administration of large doses of this drug has been used to prevent increases in systolic arterial pressure and heart rate on intubation. In this study, similar decreases in arterial pressure occurred in all four groups of patients, and it was considered that any effect of the thiopentone itself on the cardiovascular response to tracheal intubation would have been minimized by waiting 3 min before performing laryngoscopy and intubation. A large range of doses of thiopentone was used (0.9–4.0 mg kg^{-1}). This illustrates the variability of response to this drug which can be seen in a group of patients aged 70–86 yr.

The administration of alfentanil 800 or 1000 µg was followed by decreases in systolic arterial pressure and heart rate 10 min after tracheal intubation. The decreases in systolic arterial pressure and heart rate were similar for both doses, when compared with pre-induction values. However, in 10 of those patients in whom observation was continued for 20 min after tracheal intubation, systolic arterial pressure and heart rate later increased spontaneously to values above those obtained pre-induction. At this stage it was felt to be advisable to add 0.5% isoflurane to the inspired gas mixture to ensure adequate depth of anaesthesia. This decreased systolic arterial pressure to pre-induction values, although heart rate remained increased.

In those patients who received alfentanil 600 µg the pressor response to intubation was obtunded, although not abolished, without incurring marked cardiovascular depression during the first 10 min after intubation.

In this study it was decided to give fixed doses of alfentanil rather than relate dose to body weight, as there is no convincing evidence that the administration of opioids in a dose related to body weight will improve the predictability of the analgesic effect [5]. However, many anaesthetists would prefer to administer a dose of alfentanil based on body weight. Thus using the mean weight of the patients in group B, who received the 600-µg dose of alfentanil, the dose corresponds to 9.9 µg kg^{-1}. This is considerably less than the 15–30 µg kg^{-1} recommended in younger adults [1].

In conclusion, a dose of alfentanil 600 µg (9.9 µg kg^{-1}) can be used to obtund the pressor response to tracheal intubation in patients older than 70 yr who have received thiopentone and atracurium. A larger dose may abolish the pressor response, but may also cause marked cardiovascular depression during the 10 min immediately after tracheal intubation.

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CLONIDINE PREMEDICATION FOR ISOFLURANE-INDUCED HYPOTENSION

Sympathoadrenal Responses and a Computer-Controlled Assessment of the Vapour Requirement

T. E. WOODCOCK, R. K. MILLARD, J. DIXON AND C. PRYS-ROBERTS

SUMMARY

The effect of single-dose clonidine premedication on the vapour requirement for isoflurane-induced hypotension in patients undergoing middle ear or nasal surgery was evaluated in an open, controlled, randomized study. Inspired isoflurane concentration was regulated by a microcomputer-based, self-tuning control program when hypotension was required. Patients given clonidine 0.6 mg by mouth 2 h before operation required a mean inspired isoflurane concentration of 2.0% to induce hypotension (mean intra-arterial pressure 50 mm Hg) compared with 3.01% in the control group ($P < 0.05$). Five out of 10 patients in the control group required a supplementary dose of labetalol 5 mg i.v. to achieve satisfactory hypotension, compared with one of 10 patients given clonidine premedication (Fisher's exact probability, 0.07). A mean concentration of 1.4% isoflurane was required to maintain hypotension in the clonidine group, compared with 2.3% in the control group ($P < 0.01$). Plasma adrenaline and noradrenaline concentrations did not increase during induced hypotension in each group.

Isoflurane is a popular agent for induced hypotension because it is simple to use and has favourable effects on the systemic [1] and cerebral circulations [2]. During neurosurgical procedures, resistance to isoflurane-induced hypotension is unusual, and supplementary doses of a β-adrenoceptor antagonist are required only occasionally [3], possibly because plasma adrenaline and noradrenaline concentrations do not increase in neurosurgical patients during isoflurane-induced hypotension [4]. However, we have noticed that a significant proportion of patients undergoing ENT surgical procedures are relatively resistant to induced hypotension and have required labetalol to induce hypotension satisfactorily. As β-adrenoceptor antagonists can cause undesirable bradycardia following induced hypotension [5], or bronchoconstriction in susceptible individuals, we are investigating the use of alternative agents to facilitate induced hypotension.

Clonidine is an established antihypertensive agent which appears to act mainly by central α-2-adrenoceptor stimulation resulting in diminished sympathetic outflow [6]. During anaesthesia it has been shown to reduce the MAC of halothane [7,8] and to reduce the dose requirement for sodium nitroprusside-induced hypotension [9]. The purpose of the present study was to establish if single dose oral clonidine premedication would reduce the vapour requirement for isoflurane-induced hypotension in patients undergoing middle ear or nose surgery. The need for supplementary doses of labetalol was noted and plasma adrenaline and noradrenaline concentrations were measured.

PATIENTS AND METHODS

Patients aged 18–60 yr, ASA I–II, were studied during middle ear or nasal surgery requiring

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induced hypotension during anaesthesia. Patients with hypertension or obstructive airways disease were excluded. The study was approved by the local Ethics Committee, and informed consent to their participation was obtained from all subjects. Twenty patients were assigned randomly to two groups: 10 received clonidine 0.6 mg by mouth with temazepam 20 mg or 30 mg (the higher dose being used in patients weighing 70 kg or more) 2 h before surgery, while the other 10 received temazepam alone and served as a control group. Anaesthesia was induced with fentanyl 2.5 µg kg^{-1}, thiopentone 5 mg kg^{-1} and vecuronium 0.1 mg kg^{-1}. The trachea was intubated and anaesthesia was maintained with 1 % isoflurane in oxygen (Bain system) and an infusion of fentanyl 1.5 µg kg^{-1} h^{-1}. End-tidal carbon dioxide concentration was measured with a Hewlett–Packard capnometer and controlled in the range 4.5–5.0 vol % by adjusting the fresh gas flow. Hartmann's solution was infused i.v. at 150–200 ml h^{-1}.

The left radial artery was cannulated and intra-arterial pressure monitored with a Gould P23Ia transducer and a Hewlett–Packard BP module 78205A. The mean arterial pressure (MAP) signal was read through an ADC by a BBC B microcomputer, which was connected via its user port to a driving mechanism attached to the concentration selector dial of a calibrated Cyprane isoflurane vaporizer (fig. 1). When hypotension was required, a self-tuning control program using the generalized minimum-variance algorithms of Clarke and Gawthrop [10] and running in BASIC, was initiated [11–14]. The maximum available isoflurane concentration was 5 % (limited by the vaporizer). In patients who were evidently sensitive to the hypotensive effect of isoflurane, the maximum concentration was restricted to 3 % or 4 % through the keyboard as the program ran, for safety reasons.

Heart rate (HR) and MAP were recorded, and isoflurane concentration automatically adjusted, every 25 s. Data were stored on computer disc at each cycle.

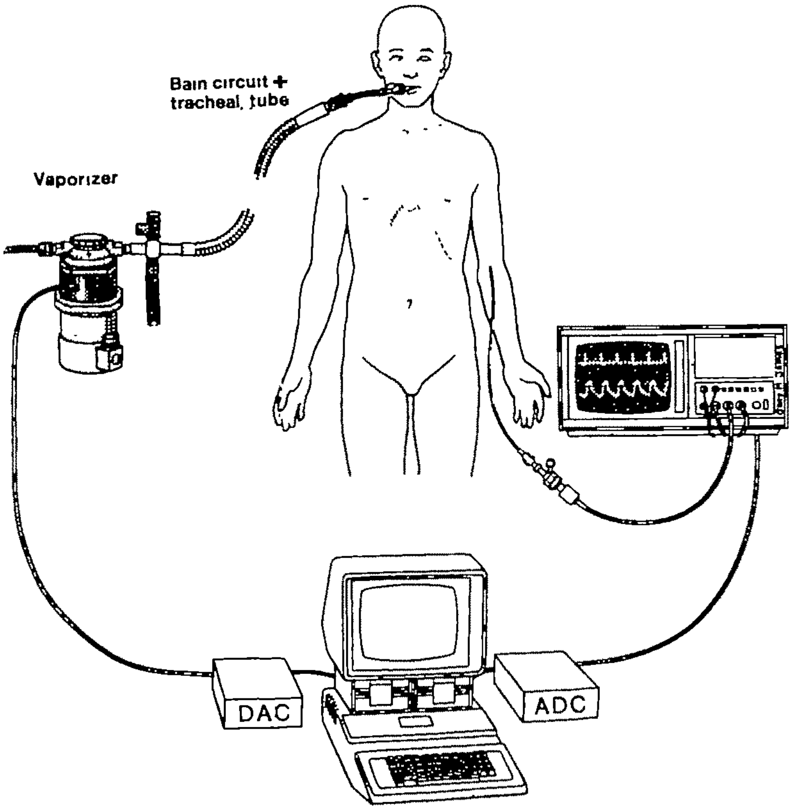

FIG. 1. Diagram of the equipment used for self-tuning control of mean arterial pressure using isoflurane as a hypotensive agent.

A supplementary dose of labetalol was used to facilitate induced hypotension when the following criteria were fulfilled: if, 10 min after initiating control, there was tachycardia (defined as a heart rate of 100 beat min^{-1} or more), or failure to achieve hypotension, labetalol 5 mg i.v. was given.

For analysis of the isoflurane dose requirement, the MAP regulation period was divided into two phases; the *induction phase* from initiation of MAP regulation to attainment of hypotension (51 mm Hg or less), and the *maintenance phase* from attainment of hypotension to the end of the MAP regulation period. Isoflurane requirement for a given phase was calculated as the mean of the concentrations selected at each 25-s cycle in that phase.

Ten millilitre of venous blood was collected in a heparinized tube containing the anti-oxidant sodium metabisulphite, stored on ice, centrifuged within 3 h of collection and analysed for plasma catecholamine concentrations (1) before induction of anaesthesia, (2) before induction of hypotension, (3) and (4) 15 and 30 min after induction of hypotension, and (5) 15 min after controlled hypotension was stopped. Plasma adrenaline and noradrenaline concentrations were measured by high pressure liquid chromatography [15].

Quality of MAP regulation in each subject was judged by calculating the standard deviation of the MAP at each 25-s cycle about the target pressure. All results are reported as the mean ±1SD. The Mann–Whitney *U* test was used to make inter-group comparisons of mean isoflurane and catecholamine concentrations, and Students's *t* test was used to compare quality of control estimates. The number of patients in each group requiring labetalol was assessed by Fisher's exact test. Probability < 0.05 was considered significant.

RESULTS

The control and treatment groups were broadly comparable in age, sex distribution, weight, type of surgery performed and duration of MAP regulation (table I).

TABLE I. *Patient characteristics*

	Control (n = 10)	Clonidine (n = 10)
Age (yr)	31±11	33±11
Sex distribution (M/F)	5/5	6/4
Weight (kg)	61±10	71±12
Type of surgery (ear/nose)	7/3	4/6
Duration of regulation period (min)	61±26	65±38

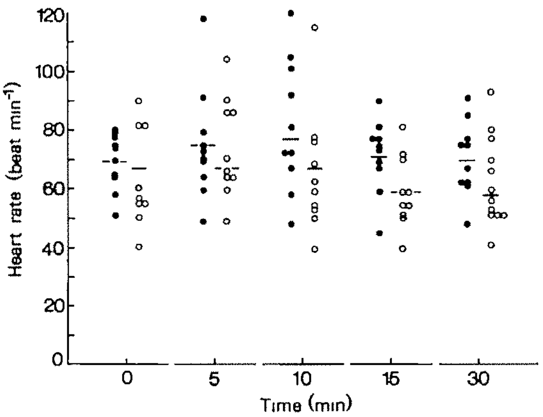

FIG. 2. Heart rate immediately before initiation of MAP regulation (time 0), then 5, 10, 15 and 30 min after initiation. Note that labetalol 5 mg was given at 10 min to six patients, four of whom had tachycardia. ● = Control; ○ = clonidine.

Before induction of hypotension HR (fig. 2) and MAP (fig. 3) were similar between groups. During induction of hypotension one patient in the control group and two in the clonidine group had HR less than 50 beat min^{-1}, while three patients in the control group and one in the clonidine group developed a tachycardia (fig. 2). Ten minutes after control was initiated, six patients required labetalol to facilitate hypotension; five of 10 in the control group, compared with one of 10 in the clonidine group (Fisher's exact probability = 0.07; ns). Of the six who received labetalol, three had both tachycardia and failure to achieve hypotension, two had only failure to achieve hypotension, and one had tachycardia only.

Mean duration of the induction phase was 9.2±4.0 min in the control group and 8.0±3.4 min in the clonidine group (ns). Induction of hypotension required a mean isoflurane concentration of 3.01±0.77 % in the control group compared with 2.0±0.79 % in the clonidine group ($P < 0.05$). Subsequent maintenance of hypotension required a mean isoflurane concentration of 2.25±0.79 % in the control group compared with 1.37±0.65 % in the clonidine group ($P < 0.01$). The mean standard deviation of the MAP about the target pressure was 2.3 mm Hg in the clonidine group, and 3.4 mm Hg in the control

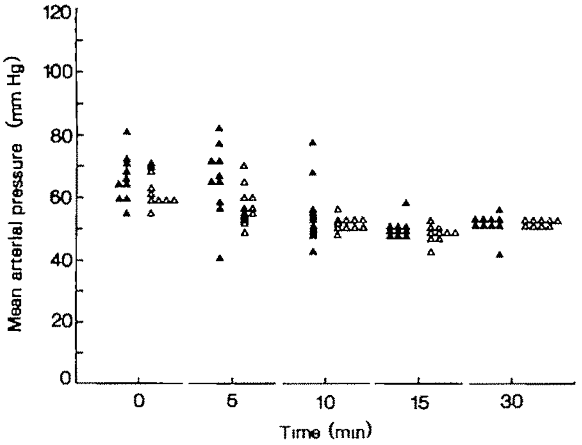

FIG. 3. Mean arterial pressure immediately before initiation of MAP regulation (time 0), then 5, 10, 15 and 30 min after initiation. Note that labetalol 5 mg was given at 10 min to six patients, five of whom had failed to achieve MAP 51 mm Hg or less within 10 min. ▲ = Control; △ = clonidine.

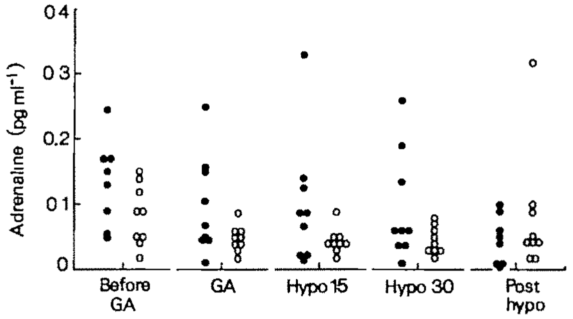

FIG. 4. Plasma adrenaline concentrations immediately before induction of anaesthesia (Before GA), under anaesthesia before induced hypotension (GA), 15 and 30 min after initiation of MAP regulation (Hypo 15 and Hypo 30) and 15 min after termination of MAP regulation (Post hypo). ● = Control; ○ = clonidine.

group (range 1.4–5.2 mm Hg). There was no intergroup difference in quality of MAP regulation.

Plasma catecholamine concentrations were generally low before induction of anaesthesia, and adrenaline concentrations were frequently at the lower limit of detection (0.02–0.08 pg ml^{-1}). They showed no significant changes during isoflurane-induced hypotension, and there was no difference in values between control and clonidine groups (figs 4, 5).

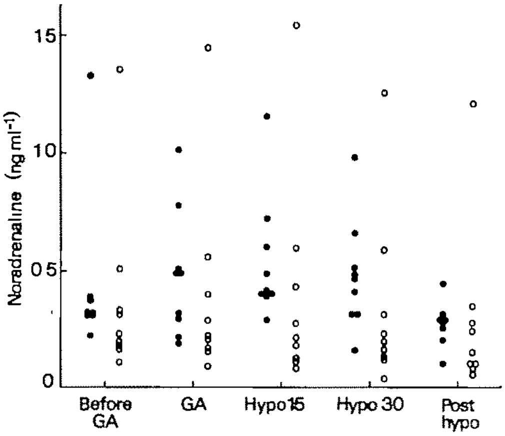

FIG. 5. Plasma noradrenaline concentrations immediately before induction of anaesthesia (Before GA), under anaesthesia before induction of hypotension (GA), 15 and 30 min after initiation of MAP regulation (Hypo 15 and Hypo 30) and 15 min after termination of MAP regulation (Post hypo). ● = Control; ○ = clonidine.

DISCUSSION

Computer control techniques can be applied in anaesthesia in situations where a variable, such as arterial pressure, is required to be tightly regulated. The self-tuning control program used in this study was based on the generalized minimum-variance algorithms of Clarke and Gawthrop [10]. It has been developed from experience with sodium nitroprusside and phenylephrine infusions [12, 16, 17], and subsequently with isoflurane delivered from a standard vaporizer modified for computer control by a positional servomechanism [11, 13]. It is designed to cope with variations in numerous patient response variables including response latency, time constant and sensitivity. Details of the program, its development and implementation have been published previously [11–14]. The mathematical principles applied in this self-tuning program are outlined in the Appendix. Self-tuning control of isoflurane concentration to regulate mean arterial pressure is a strategy which gives an objective quantification of the vapour requirement for induced hypotension. It performs as well as a trained anaesthetist using manual control of the vaporizer dial, when the standard deviation of MAP about the target pressure is of the order of 3.5–4.4 mm Hg [13]. It has proven to be a suitable tool for evaluating the influence of clonidine premedication on isoflurane-induced hypotension. The isoflurane requirements for induction and maintenance of hypotension in our control group are comparable to those reported by other workers using manual control [1–3]. The quality of control in this study was satisfactory by the criterion of standard deviation of MAP about the target pressure.

This is the first report of the effect of a single dose of clonidine upon the vapour requirement for isoflurane-induced hypotension in surgical patients. Isoflurane is particularly suited to hypotensive anaesthesia because of its favourable effects on the balance of cerebral blood flow and metabolism [2,18]. As nitrous oxide tends to stimulate cerebral metabolism [19,20] and may negate any protective effects of depressant agents [21] we have used isoflurane in oxygen, with analgesia provided by a fentanyl infusion, in our anaesthetic technique.

Plasma catecholamine concentrations are increased during hypotension induced with vasodilators such as sodium nitroprusside [22,23] and resistance to hypotension is well described [24, 25]. This is commonly treated with a β-adrenoceptor antagonist [25] or the combined α- and β-adrenoceptor antagonist labetalol [24]. In contrast, MacNab and colleagues [4] found that increase in plasma catecholamine concentration does not occur with isoflurane-induced hypotension in patients with intracranial aneurysm, and the same group reported that supplementary doses of β-adrenoceptor antagonists were required in only eight of 96 patients [3]. Our study has confirmed the absence of catecholamine response to isoflurane-induced hypotension in non-neurosurgical patients, but we found that approximately 50% of patients without clonidine premedication required a supplementary agent to facilitate induced hypotension during ENT surgery. This difference is probably related to the power of the surgical stimulus during the hypotensive period and perhaps to different criteria for resorting to a supplementary agent. It also suggests that resistance to induced hypotension is not solely dependent on high concentrations of circulating adrenaline and noradrenaline. The absence of a catecholamine response to isoflurane-induced hypotension is probably a non-specific consequence of deep anaesthesia, comparable to the reduction of the stress response by enflurane during surgery [26] and by isoflurane during cardiopulmonary bypass [27].

Clonidine is an α-2-adrenoceptor agonist which is indicated in the treatment of hypertension, menopausal flushing and migraine prophylaxis. It is not a drug of first choice in the management of hypertension as it causes drowsiness, and occasional rebound hypertension upon withdrawal of chronic therapy [6]. Rebound hypertension does not occur after a single dose, and a sedative effect is desirable in a drug used for anaesthetic premedication. Clonidine also produces analgesia at the spinal cord level [28]. Peak plasma concentrations are achieved, and a reduction in resting noradrenaline concentrations occurs, approximately 2.5 h after oral administration [29]. It is therefore to be expected that it would potentiate halothane [7,8], thiopentone [30] or opioid anaesthesia [31], and facilitate induced hypotension [9].

The results of our study show that single dose oral premedication with clonidine 0.6 mg in surgical patients significantly reduces the vapour requirement for isoflurane-induced hypotension, although it does not entirely obviate the need for further supplementary agents to facilitate induced hypotension. We found no significant difference in plasma catecholamine concentrations between the control and clonidine-treated groups at any stage.

We conclude that clonidine, a drug which has no effect upon airway resistance, may be a suitable alternative agent to facilitate induced hypotension when the β-adrenoceptor antagonists are contraindicated. Our anaesthetic technique did not include any vagolytic agents and we were, therefore, not surprised to find heart rates of less than 50 beat min^{-1} in three patients (one control, two clonidine) during anaesthesia. No other side effects attributable to the use of clonidine premedication were observed in this small study.

APPENDIX

The principal steps in the self-tuning program are as follows: If MAP values $y(t), y(t-1), y(t-2), \ldots$ and isoflurane inspired concentrations $u(t), u(t-1), u(t-2), \ldots$ occur at present and previous samples $t, t-1, t-2, \ldots$ the following equation is used to estimate the parameters of the controlled system (i.e. patient AP):

$$\varphi(t) = f_0 y_F(t-2) + g_0 u(t-2) + g_1 u(t-3) + g_2 u(t-4) + d.1 \quad (1)$$

where $y_F(t-2) = 3.52772647 * y(t-2)$, and f_0, g_0, g_1, g_2, d are the unknown parameters. $\varphi(t) = y_F(t) - 0.71653131 * y_F(t-1)$ is an auxiliary output and is controlled to be at the set point $w(t)$ two sample times from the current sample time t. The equations are such that the actual output $y(t)$ will follow the auxiliary output exponentially with time constant of three sample times. Rewriting (1) as a prediction of $\varphi(t+2)$, direct substitution of $t+2$ for t gives:

$$\varphi(t+2) = f_0 y_F(t) + g_0 u(t) + g_1 u(t-1) + g_2 u(t-2) + d \quad (2)$$

(Two-step-ahead prediction is required to allow for a transportation lagtime between a change of inspired concentration at the vaporizer and the start of an arterial pressure response in the arteries.) So if we choose $u(t)$ to be:

$$u(t) = -(f_0 y_F(t) + g_1 u(t-1) + g_2 u(t-2) + d - w(t))/g_0 \quad (3)$$

We achieve $\varphi(t+2) = w(t)$ and get the required response for $y(t)$.

To estimate the parameters in the control law (3) the following recursions are performed as soon as a new sample of MAP $y(t)$ becomes available:

Rewriting equation (1) as the scalar product of two array vectors:

$$\begin{aligned}\varphi(t) &= (f_0, g_0, g_1, g_2, d).(y_F(t-2), u(t-2), u(t-3), u(t-4), 1)\\ &= P(t)^T.Z(t)\end{aligned}$$

where $P(t)^T$ is the transpose of a column vector of the parameters, $P(t)^T = (f_0, ,.,., d)$, and $Z(t)$ is a column vector of the data, $Z(t) = (y_F(t-2),., ,.,1)^T$, then the prediction error of the estimates obtained from the previous sample time is:

$$E = \varphi(t) - P(t)^T Z(t)$$

let:

$$z = Z(t)^T C(t) Z(t)$$

where $C(t)$ is a (5×5) covariance matrix that specifies the accuracy to which the estimates are determined.

Let

$$n = E^2/L(t)$$

$$f^{-1} = 1 + (1+r)((z(v+1)n)/((1+z)(1+z+n)))$$

$$e = f - (1-f)/z.$$

New estimates:

$$P(t+1) = P(t) + C(t) Z(t) E/(1+z)$$

new covariance:

$$C(t+1) = C(t) - C(t) Z(t) Z(t)^T C(t)/(e^{-1} + z)$$

$$L(t+1) = f(L(t) + E^2/(1+z))$$

rename

$$v = f(v+1)$$

(at the next sample time $t+1$ will become t). To start the recursions the following prior values are used the first time the estimates are calculated: $C(1)$ is a diagonal matrix with 100s on the main diagonal, 0s elsewhere, $P(1)^T = (0.1, -0.9, 0.1, 0.1, 0.1)$, $L(1) = 100$, $v = 3$, $r = 0.05$. For further details see Karny and colleagues [32] in the first instance. In fairness to the reader, many other calculations are required (see, for example reference [14]).

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ANAESTHETIC UPTAKE AND ELIMINATION: IS THERE A DIFFERENCE BETWEEN HALOTHANE AND ISOFLURANE IN THE DOG?

A. M. ZBINDEN, D. A. THOMSON, D. R. WESTENSKOW, F. FREI AND J. MAERTENS

SUMMARY

In two groups of dogs, the uptake and elimination of halothane and isoflurane were studied using a closed-loop anaesthetic system which automatically controlled end-tidal halothane and isoflurane partial pressures at equi-MAC concentrations. Haemodynamic and respiratory variables were recorded and the anaesthetic partial pressures were measured in the inspired and expired air, as well as in the arterial, cerebrovenous and mixed venous blood. The controller delivered a higher inspired partial pressure of halothane than of isoflurane to compensate for the higher blood/gas partition coefficient. The partial pressures of halothane in the arterial, cerebrovenous and mixed venous blood increased at rates similar to those of isoflurane. During 160 min of uptake, the cerebral venous partial pressures remained significantly lower than the arterial partial pressures for both agents. On discontinuation of the anaesthetic, the partial pressures of halothane and isoflurane decreased at equal rates in arterial, cerebrovenous and mixed venous blood, and in end-tidal gas. It was concluded that the rate of uptake of isoflurane is more rapid than that of halothane from the alveolar space to the blood, but not from the blood to brain tissue. The rates of elimination from brain tissue and from blood were found to be similar for both agents.

Volatile anaesthetics are characterized by well defined relationships between their partial pressures in brain tissue and anaesthetic effect [1], and by a narrow therapeutic range [2, 3]. The ultimate goal of inhalation anaesthesia should be to obtain, rapidly and safely, an adequate partial pressure of the volatile anaesthetic in the brain. Isoflurane, because of its reportedly lower partition coefficients (blood/gas and tissue/blood), is considered to have a more rapid pharmacokinetic profile than halothane [4]. Although brain tissue partial pressure cannot be measured directly in patients, the end-tidal partial pressure can be monitored continuously [5] and should be indirectly related to the brain tissue partial pressure. In this study, a feedback system [6] was used to adjust automatically the flow of the anaesthetic agent into a closed breathing system, thereby maintaining the end-tidal partial pressure constant at the desired value. Using this system the uptake and elimination of halothane and isoflurane have been studied by following their partial pressures in arterial, cerebrovenous and mixed venous blood.

MATERIALS AND METHODS

Twelve mongrel dogs (24–39 kg) were premedicated with fentanyl 40 μg kg^{-1} and droperidol 2 mg kg^{-1} i.m. 1 h before placement of instrumentation. Anaesthesia was induced with pentobarbitone 12–15 mg kg^{-1} i.v. and the trachea intubated. The dogs were placed supine and the lungs ventilated with 100% oxygen at 12 b.p.m. Tidal volume was adjusted to maintain arterial carbon dioxide (Pa_{CO_2}) at 5.3 kPa. To provide basal anaesthesia during the preparation, droperidol 30 mg and fentanyl 600 μg were given initially and followed

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TABLE I. *Physiological values (mean ± SD) in both groups of dogs* (n = *6*) *at the beginning (0 min) and end (220 min) of the experiment*

	Halothane group		Isoflurane group	
	Beginning	End	Beginning	End
Arterial blood				
Haemoglobin (%)	13.0±0.5	12.8±0.6	12.0±1.7	11.4±1.2
pH	7.26±0.3	7.31±0.8	7.29±0.03	7.34±0.04
BE (mmol litre^{-1})	−5.23±4.5	−7.40±2.44	−4.40±1.2	−4.02±2.2
P_{CO_2} (kPa)	5.36±0.67	4.83±0.77	6.00±0.48	5.29±0.7
P_{O_2} (kPa)	61.87±2.40	61.47±7.6	62.53±5.87	60.67±7.87
Temperature (°C)	37.4±1.6	37.7±0.3	37.8±2.29	38.0±0.3
Pulm. A–V shunt (%)	11.2±3.5	9.3±2.5	10.4±5.3	12.0±3.1
Pulm. deadspace (%)	59±6.3	59±4	63±1.4	67±4
Weight (kg)	28.2±7.1		31.8±4.8	
Blood/gas partition coefficient	2.4±0.3	2.6±0.3	1.3±0.1	1.3±0.2

by a continuous infusion of fentanyl 15 μg kg^{-1} h^{-1}. Pancuronium 60 μg kg^{-1} h^{-1} was also given. Fluid volume was maintained with an infusion of physiological saline 2 ml kg^{-1} h^{-1}. The dogs were heparinized with heparin 500 iu kg^{-1}. Temperature was maintained at 37 °C using a heated, thermostatically controlled, operating table. Haemodynamic monitoring consisted of ECG, arterial pressure (via a femoral artery catheter), central venous and pulmonary artery and pulmonary capillary wedge pressures (using a thermistor-tipped Swan–Ganz catheter inserted to the internal jugular vein). Iced injectate (5 ml) was used to measure cardiac output in triplicate with an Edwards 520 cardiac output computer. The retroglenoid vein was isolated, all branches were ligated except the one coming from the brain and a 1-mm diameter catheter was advanced into the sagittal sinus for sampling cerebrovenous blood. Correct placement of the catheter was verified by using contrast medium injected to the catheter.

The partial pressure of the volatile anaesthetics in arterial, cerebrovenous and mixed venous samples was determined using a head-space gas chromatographic (GC) method [7]. A tonometer was used to create blood with a well-defined partial pressure of the volatile anaesthetic for each dog before and after the experiment. Thus for each dog an average individual standard curve was obtained from these two curves relating GC counts to partial pressure. During the study, the GC counts were determined in the blood samples and the partial pressure was read from the average standard curve. A Beckman LB-2 infra-red analyser, the accuracy of which had been verified previously [8] was used for determination of the partial pressure in the inspired and expired gas as well as at the outlet of the tonometer. The partial pressure in the gas phase could then be directly compared with the partial pressure in the blood phase. The blood/gas partition coefficient was determined for each dog (table I).

Following surgical preparation and after baseline haemodynamic measurements, six dogs received halothane at an end-tidal partial pressure of halothane 6.44 mm Hg (1 MAC for dogs; 0.87 vol% at 740 mm Hg barometric pressure) and another six dogs were given isoflurane 9.47 mm Hg (1 MAC for dogs; 1.28 vol% at 740 mm Hg barometric pressure) [9]. A feedback controlled anaesthesia delivery system, developed in our laboratory [6], was able to achieve the desired end-tidal partial pressure within less than 3 min within a range of 0.70±0.14 vol% for halothane and 1.2±0.1 vol% for isoflurane without overshooting, and to maintain it during the subsequent uptake period. Measurements of anaesthetic partial pressures, and haemodynamic and respiratory variables were performed. After 160 min of uptake, the anaesthetic was removed from the circuit by switching a 1.0-litre activated charcoal absorber into the breathing circuit. Elimination continued for a further 60 min, and the standard measurements were performed at 161, 162, 163, 166, 169, 180, 200 and 217 min.

To compare the two agents, the arterial, cerebrovenous and mixed venous partial pressures were expressed as fractional percentages of the end-tidal partial pressure values during the uptake phase and, for the elimination phase, of

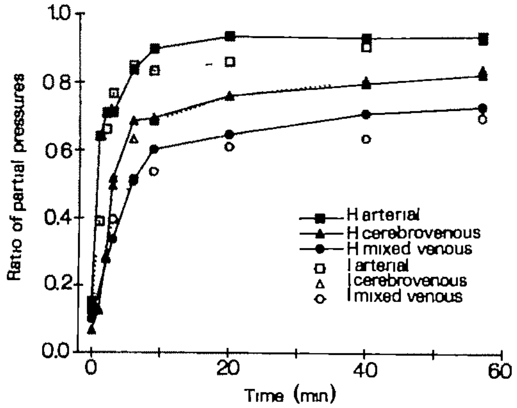

FIG. 1. First 60 min of uptake of halothane (H) and isoflurane (I). Ratios of partial pressure of halothane and isoflurane (in the arterial, cerebrovenous and mixed venous blood) to the end-tidal partial pressures.

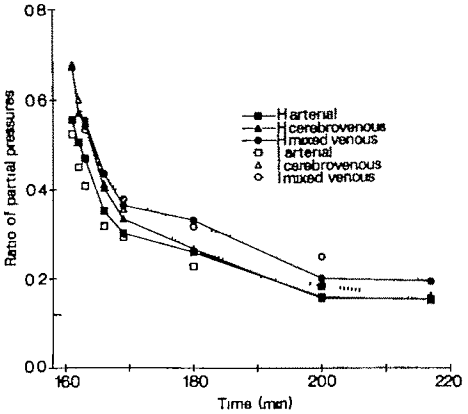

FIG. 2. First 60 min of elimination of halothane (H) and isoflurane (I). Ratios of the partial pressures of halothane and isoflurane (in the arterial, cerebrovenous, and mixed venous blood) to the end-tidal partial pressures at the end of uptake. The slight difference between the halothane and isoflurane groups in the inspired partial pressure was accounted for by subtracting the actual inspired partial pressure from that of each compartment and the mean inspired pressure during the elimination phase from the end-tidal partial pressure at the end of the uptake period.

the value of the end-tidal partial pressure at the start of elimination. In the calculations, the incomplete removal of the anaesthetic by the charcoal was accounted for by subtracting the inspired partial pressure from the arterial, cerebrovenous and mixed venous partial pressure during the elimination phase and the mean inspired partial pressure of the elimination phase from the end-tidal partial pressure value at the start of the elimination (figs 1, 2).

RESULTS

In both groups of dogs, 95% of the desired end-tidal partial pressure (1 MAC) was obtained in less than 3 min and remained constant for 160 min. The inspired partial pressure, as adjusted by the feedback-control system, was significantly higher in the halothane group than in the isoflurane group. The partial pressures of halothane and isoflurane in the arterial, cerebrovenous and mixed venous blood increased at equal rates (fig. 1). The arterial partial pressures of halothane and isoflurane remained significantly lower than the end-tidal partial pressures, and the cerebrovenous partial pressures remained lower than the arterial partial pressures. In two dogs of each group, a second uptake period was started at 220 min to determine if the arterial to cerebrovenous gradient persisted. Approximately 5 h after the start of the second uptake period, the gradient between the arterial and cerebrovenous blood approached zero for both agents.

On discontinuation of the anaesthetic, the inspired concentration decreased immediately to an average value of 0.09 vol% halothane and 0.02 vol% isoflurane. When the slight difference in inspired concentration was accounted for, the partial pressure of halothane in the arterial, cerebrovenous and mixed venous blood decreased at a rate equal to that of isoflurane (fig. 2). The

TABLE II. *Comparison of haemodynamic variables (mean ± SEM) measured during halothane (H) and isoflurane (I) anaesthesia, during 160 min of uptake and during 60 min of elimination*

	Heart rate (beat min^{-1})		Arterial pressure (mm Hg)		Cardiac output (litre min^{-1})	
	H	I	H	I	H	I
Uptake	86±4	94±4	74±3	73±2	3.9±0.2	3.4±0.2
Elimination	94±6	90±6	67±5	59±4	2.7±0.3	2.5±0.3

differences between cerebrovenous, arterial and end-tidal partial pressures were smaller during elimination than during uptake for both agents.

Table II compares heart rate, arterial pressure and cardiac output for each period. A Mann–Whitney test with a significance level of 0.05 was used to compare haemodynamic indices between the halothane and the isoflurane groups. Significant differences ($P < 0.05$) between halothane and isoflurane could not be found for any variable.

The values of additional indices (table I) were determined at the beginning and end (220 min) of each investigation.

DISCUSSION

The uptake and elimination of halothane by the lung have been compared [10] with those of isoflurane by determining the $F_E:F_I$ ratio during, and after, the simultaneous administration of enflurane, halothane, isoflurane, methoxyflurane and nitrous oxide. The uptake of isoflurane was slightly more rapid than that of halothane, but was still considerably slower than that of nitrous oxide. The rates of elimination of halothane and isoflurane were virtually the same, that for halothane being slightly more rapid during the last phase of the elimination from the slow compartment. These results are surprising, as it would be expected that isoflurane would have faster kinetics as a result of its lower blood/gas solubility coefficient. In the present study, the blood/gas partition coefficients could be determined as 2.6 ± 0.3 for halothane and 1.3 ± 0.1 for isoflurane—values which are in agreement with those reported in man (2.3 for halothane [4] and 1.4 for isoflurane [11]). Obviously, the blood/gas partition coefficient is not the sole determinant of the speed of change in the $F_E:F_I$ ratio of volatile anaesthetics. The uptake and elimination to and from the organs seem to be important additive factors. Furthermore, if the uptake and elimination of an agent is rapid between lung and blood (because of its low blood/gas partition coefficient), this does not necessarily mean a rapid transfer between blood and brain tissue. Tissue uptake of volatile anaesthetics is determined by the perfusion of the tissue and the tissue/blood partition coefficient of the anaesthetic [4]. The brain/blood partition coefficient has recently been reported to be 1.74 ± 0.05 for isoflurane and 2.03 ± 0.04 for halothane in a group of young adults (20–50 yr) [12]. In previous investigations in man a greater difference has been reported (2.57 for halothane [4] and 2.00 for isoflurane [13]). Thus the difference in the blood/gas partition coefficient between halothane and isoflurane is much larger than that of the brain/blood partition coefficient. Enflurane, as another example, has a considerably lower brain/blood partition coefficient than isoflurane (for middle-aged adults it is 1.28 ± 0.05 for enflurane and 1.65 ± 0.06 for isoflurane), although its blood/gas partition coefficient is higher than that of isoflurane (1.91 for enflurane and 1.37 for isoflurane) [12]. Therefore, it is not possible to draw conclusions about the brain/blood partition coefficient from knowledge of the blood/gas partition coefficient. This explains why the pulmonary uptake and elimination of isoflurane may be faster than that of halothane and why neither the brain nor the whole body uptake and elimination of isoflurane are faster than those of halothane.

In this study, the rate of uptake from the arterial blood to brain tissue was found to be similar for halothane and isoflurane. The rates of elimination from the brain to the blood, and from the blood to the lungs, were also found to be similar for both agents. The unexpectedly slow elimination of isoflurane from the brain compared with that of halothane cannot be explained solely by the relatively high brain/blood solubility coefficient isoflurane. Halothane is metabolized to a considerable extent [14] and this contributes significantly to the whole body elimination of halothane and thus to the rapid decrease of halothane in the arterial blood reaching the brain.

Elimination from brain tissue is also dependent on cerebral blood flow; the higher the blood flow, the more rapid the elimination. Investigations by Theye and Michenfelder [15] Cucchiara, Theye and Michenfelder [16] have compared CBF in dogs under both halothane and isoflurane anaesthesia. CBF was increased by 43% and 33%, by 1.13 MAC halothane and 1.09 MAC isoflurane, respectively. Stullken and colleagues [17], however, found almost identical CBF values in dogs for 1 MAC halothane, enflurane or isoflurane, provided arterial pressure was kept constant. We did not measure CBF, but arterial pressure and cardiac output were similar in both of our groups, thus suggesting nearly identical cerebral blood flows in both groups. In man, Murphy, Kennell and Johnstone [18] demonstrated a greater cerebral vasodilator effect of halothane—which would point to even more rapid kinetics for halothane in man.

Direct tissue determination of the anaesthetic concentration has been performed by Cohen, Chow and Mathers [19] using ^{14}C-labelled halothane and an autoradiographic *in vitro* technique to study the distribution of halothane in the brain of dogs. The uptake varied considerably between different anatomical areas of the brain tissue as a result of differences in lipid content, blood flow and other unknown factors. Recently, nuclear magnetic resonance has been introduced to measure anaesthetic concentration in tissue and *in vivo*. Wyrwicz and co-workers [20, 21] observed an exceptionally slow elimination rate for both halothane and isoflurane. However, it was not stated whether the obtained signal originated from pure brain tissue or if other compartments, such as orbital fat—which might explain the slow kinetics—were also included.

In this study, another *in vivo* method of determining the brain anaesthetic concentration was used. It measures the concentration in cerebrovenous blood assuming equilibrium between brain tissue and capillary blood. This assumption is based on the theories of Zuntz [22] and Von Schrötter [23] for inert gas kinetics in the body. According to these theories, diffusion is not a limiting factor in the equilibrium process and all blood which flows through a tissue compartment partakes in this process [24]. In other words, the anaesthetic partial pressure in the cerebrovenous blood should be equal to the brain tissue pressure after the initial uptake period.

It is important to determine partial pressure—not content—of the volatile anaesthetic in the blood as the blood/gas partition coefficient may vary considerably within and between individuals, depending mainly on the lipid content in their blood [25]. Our gas chromatography method [7] compensates for interindividual and, to some extent, for intraindividual variability in the blood/gas partition coefficient by obtaining standard curves both before and after each investigation in each dog.

According to known data for cerebral perfusion rate and tissue/blood partition coefficients, equilibrium between cerebrovenous and arterial anaesthetic partial pressures should occur after about 15–20 min [4, 13]. However, in our study, even after 160 min of uptake, the cerebrovenous partial pressures for both agents were 9% lower than the arterial, and the gradient disappeared only after 5 h. During elimination, the cerebrovenous partial pressure was only slightly greater than the arterial. This difference between uptake and elimination can be explained by the fact that the desired end-tidal, or arterial, partial pressure can be achieved rapidly by unlimited increases in the inspired partial pressure during uptake. A similar process is not possible during elimination as the inspired concentration can only be reduced to zero at most. Consequently, the end-tidal or arterial partial pressure reaches the desired value (zero) more slowly, and an arterial–cerebrovenous pressure gradient cannot be built up to the same extent as during uptake.

A persisting arterial–cerebrovenous gradient could also be explained by a difference of the blood/gas partition coefficient in arterial blood compared with that in the venous blood, as a result of different partial pressures of various gases. The arterial–venous gradients of the oxygen and carbon dioxide partial pressures may affect the gas chromatographic analytical method, although we think we have ruled out these factors [7]. Another reason for a gradient could be diffusion from the brain to an adjacent slow compartment—as has been shown for the kidney [26], but not for the brain. Venous admixture from a slow compartment could also explain the gradient. Cerebral drainage in the dog is different from that in man, but the technique used in this study to collect true cerebrovenous blood from dogs has been used previously by Allott, Steward and Mapleson [26]. Rapela and Green [27] have described cerebrovenous sampling from the sagittal sinus as safe from venous admixture except for irrelevant admixture from the diploë. In this study, correct placement of the catheter in the sagittal sinus was ensured after extensive anatomical studies and using angiography. We found that slight venous admixture may occur from the periorbital area, which is comparable to the human circulation. The observed persistence of a small gradient, however, can only partly be explained by venous admixture from slow compartments. The size of such a compartment can be calculated assuming a cerebral perfusion of 0.5 litre min^{-1}/kg of tissue [26], a brain weight of 0.28% of total body mass = 0.078 kg [28], and an average body weight of 28.2 kg in the halothane group; a total cerebral blood flow of 0.039 litre min^{-1} results. After 160 min the arterial–cerebrovenous gradient was 9% of the arterial partial pressure, which might be attributed to an admixture of 0.0035 litre min^{-1} blood of zero partial pressure (in reality, saturation of fat tissue is about 4% at that time, which is negligible). Assuming 0.025 litre min^{-1}/kg of fat tissue perfusion, this would correspond to the drainage from 0.14 kg of fat tissue, which is about a volume of 150 ml of fat tissue, a compartment which is almost twice as big as that of the average dog brain. Permanent binding to structures within the brain tissue might be another reason for the persistence of the gradient.

Performance studies in animals and patients are but an indirect, although clinically relevant, technique with which to compare the speed of uptake and elimination of volatile agents. Isoflurane has been found to be faster than [29–31], equal to [32] or slower than [33, 34] halothane. A multitude of factors may affect the results of such studies: (1) In a rebreathing system, the inspired concentration may be unpredictable as a result of absorption of the volatile agent to components of the breathing system [13, 35]. (2) Pulmonary uptake and elimination may vary, depending upon ventilation and perfusion [4]. (3) Because of concentration-dependent metabolism, different results may be obtained depending on whether trace concentrations of anaesthetic concentrations are used [11, 25, 36, 37]. (4) Metabolic products from halothane, such as bromide, may be pharmacodynamically active [38, 39]. (5) Brain tissue uptake and elimination depend on the brain tissue/blood partition coefficient and CBF, as already mentioned.

In summary, when the pharmacokinetics of halothane is compared with that of isoflurane, the low blood/gas partition coefficient of isoflurane points to a more rapid pulmonary uptake of isoflurane in comparison with that of halothane. If, however, the inspired concentration of halothane is augmented sufficiently relative to that of isoflurane, this difference can be overcome. The speed of uptake and elimination to and from the brain is the same for both agents. Furthermore, total body elimination is equally fast for isoflurane and halothane. Other factors, such as metabolism and the individual organ tissue/blood partition coefficient, are as important as the blood/gas partition coefficient. This explains the rapid kinetics of halothane despite its high blood/gas partition coefficient, the importance of which has often been overstressed.

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FAILURE OF EXTRADURAL BLOCKADE IN OBSTETRICS

A New Hypothesis

V. P. S. NARANG AND S. P. K. LINTER

Lumbar extradural analgesia is a well-established method of providing pain relief during labour. However, analgesia may be complete in only 80% of patients initially [1], and many of the remaining patients may feel that the extradural analgesia has been a complete failure because of partial or complete unilateral blockade.

The reported incidence of unsatisfactory blockade varies widely: between 1.5% [2] and 21% [3] of extradural blocks may be unilateral. Midline septa [4], fibrous adhesions [4, 5], dural folds [6] and separate anterior/posterior extradural spaces [6] have all been proposed to account for the inadequacy of the analgesia by restricting the spread of anaesthetic solution. Paravertebral passage of the catheter and passage into the anterior extradural space [7] has also been considered, but is said not to occur if the length of catheter in the extradural space is less than 4 cm [8].

While these factors may account for some failures, we felt that the commonest cause of a unilateral block was incorrect, lateral placement of the catheter by the operator. On account of the triangular nature of the extradural space [9], any divergence from the midline (when using a midline technique) will make lateral placement of the catheter increasingly likely as the skin–extradural space distance (S–EDS) increases (fig. 1). Lateral placement of the catheter is more likely to produce a unilateral block as a result of uneven or restricted spread [1].

SUMMARY

Three-thousand and eleven consecutive obstetric extradural blocks were evaluated retrospectively. The distance from the skin to the extradural space was correlated with the incidence of unilateral blockade. There was a significant correlation ($P < 0.001$) between an increasing distance and increased incidence of unilateral block. We propose that this is because of the topography of the extradural space, and because of the deviation of the tip of the needle from the midline (when using a midline approach).

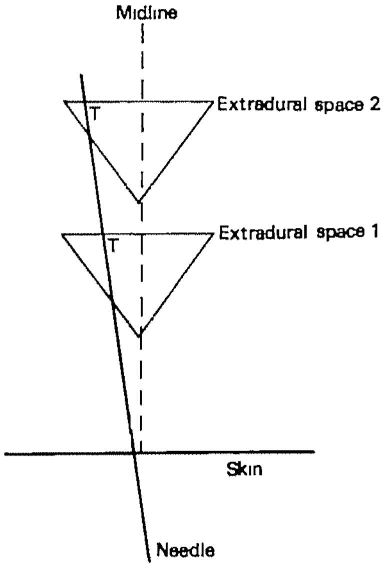

FIG. 1. Diagram showing increasing lateral displacement of the tip of the needle (T) as the skin-to-extradural space distance increases from extradural space 1 to 2.

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PATIENTS, MATERIALS AND METHODS

To investigate this hypothesis, 3011 consecutive extradural procedures were reviewed. There were 26 operators during a 4-year period. All were members of the junior staff. All extradural blocks were performed after the onset of labour. The midline approach in the sitting position was used in all patients and the blocks were performed at either the L2–3, L3–4, or L4–5 spaces. Tuohy needles graduated at 1-cm intervals were used and the extradural space identified by loss of resistance to either air or saline. Skin to extradural space distance was recorded. Graduated polyvinylchloride extradural catheters (Portex Ltd or Vygon Ltd) were passed into the extradural space to a depth of 2–3 cm. Uniformity of recording was encouraged using a standardized "box type" extradural form.

After an initial test dose, the first dose of 0.25% bupivacaine plain 6–8 ml was injected through the catheter.

An unsatisfactory block was defined as one that necessitated further manoeuvres (either increased volume or increased concentration with change of position, or re-introduction of the catheter) within the first 40 min because of unilateral pain either from a complete or partial unilateral block.

RESULTS

Three thousand and eleven patients were reviewed. Table I shows the total number of blocks at various skin to extradural space distances, the number of unsatisfactory blocks, and the distribution of unsatisfactory extradural blocks as a percentage of the total number of block at each depth. Using Spearman's rank correlation, there is a significant ($P < 0.001$) correlation between the incidence of unilateral blocks and the S–EDS distance. The regression coefficient is 0.98.

TABLE I. *Details of extradural blocks performed. EDS = extradural space*

Distance Skin–EDS (cm)	Total no. extradurals	Unsatisfactory blocks	
		No.	(% of total number at each distance)
2– < 3	4	0	0
3– < 4	478	60	14.4
4– < 5	1442	203	16.4
5– < 6	835	153	22.4
6– < 7	167	52	45.2
7– < 8	60	23	62.2
8– < 9	24	10	71.4
9– < 10	1	0	0

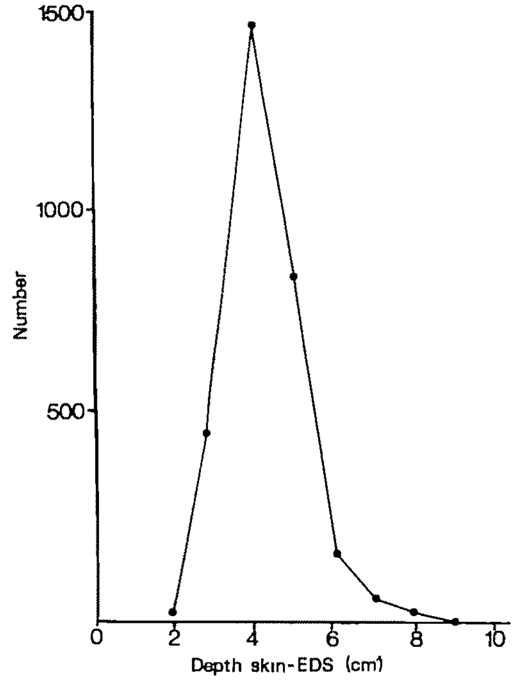

FIG. 2. Distribution of skin-to-extradural space distances.

The distribution of the S–EDS distances are shown in figure 2. Analgesia was initially complete in 2510 patients.

DISCUSSION

The distribution of the skin-extradural space distance agrees with the original study of Gutierrez [10] and other subsequent investigations [11, 12]. However, there is a significant correlation ($P < 0.001$) between an increasing S–EDS distance and an increasing incidence of unilateral blocks.

We propose that it is the deviation of the tip of the needle (when using a midline approach to the lumbar extradural space) that leads to lateral placement of the catheter and, because of the topography of the extradural space, an increased chance of producing a unilateral block. Anatomical abnormalities are rarely to blame for failed extradural blocks.

Experimentally, Bromage [1] consistently produced unilateral analgesia in dogs by implanting catheters laterally in the extradural space. Also using dogs, Usubiaga, Reis and Usubiaga [7] concluded that unilateral analgesia was caused by the extradural catheter curling around the dural tube into the anterior portion of the extradural space, from where diffusion of local anaesthetic may be less symmetrical. Bromage suggested that extradural catheters should ideally be close to the midline in the posterior extradural space, "so that diffusion of the injected local anaesthetic would be even and symmetrical".

However, lateral catheter placement within the extradural space is not the complete answer. Transforaminal escape of the catheter has been reported [13, 14]. Escape has occurred predominantly when an excessive length of catheter (5–10 cm) had been inserted to the extradural space. It may be that, even when a moderate length of catheter (2–4 cm) has been inserted to the extradural space, if the tip of the needle has come to lie laterally within the space the chances of transforaminal catheter escape are still higher than when the catheter is placed posteriorly.

There are other factors that are known to affect extradural blocks. Shanks [15] described unilateral analgesia occurring in the presence of radiographic evidence of bilateral and even spread within the extradural space. It has been suggested that local anaesthetic drugs do not penetrate each nerve trunk with a similar facility and that analgesia is therefore often incomplete or segmented on many occasions [16]. This would explain the presence of missed segments, that may have cranio–caudal boundaries.

Fat within the extradural space may also play a part in the aetiology of unsatisfactory extradural blocks. Palmer and colleagues [11] showed a direct relationship between the skin to extradural distance and body weight. They suggested that subcutaneous tissue may account for much of the variation in extradural space distance. Possibly, there is also the same variation of fatty tissue within the extradural space itself, greater amounts making an even distribution of local anaesthetic solutions less likely.

Labat [16] suggested that the midline approach is the most commonly used and preferred route. However, the paramedian approach is used successfully by some anaesthetists. Presumably, lateral catheter placement still occurs with this technique (as do unilateral blocks). There are no figures to confirm whether unilateral blocks occur more or less frequently with this approach.

There are undoubtedly many factors responsible for unilateral extradural analgesia and the anaesthetist frequently has no way of knowing their relative importance in any individual patient. However, we believe that one of the fundamental factors governing the development of a unilateral block is lateral catheter placement, following deviation of the tip of the extradural needle from the midline.

The practical importance of this study is that, if the extradural space has not been identified before a depth of 6 cm, then there is > 40% chance of producing an unsatisfactory block.

Redirection or re-insertion at an early stage may produce better analgesia more quickly for the parturient.

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ENDOCARDIAL VIABILITY RATIO AND ISCHAEMIC DYSFUNCTION OF THE LEFT VENTRICLE DURING HALOTHANE ANAESTHESIA§

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SUMMARY

In normal hearts, the critical value of the endocardial viability ratio (EVR) is thought to be less than 0.5. As myocardial regional dysfunction is a sensitive index of subendocardial ischaemia, the relationship between EVR and regional function has been studied in an experimental model of coronary artery constriction. In 13 dogs anaesthetized with halothane (0.5–2.0% inspired concentration), diastolic and systolic pressure time indices were obtained by planimetry, and their ratio (EVR) correlated with regional function. Halothane alone caused a significant reduction in EVR from 1.38 ± 0.08 to 1.15 ± 0.04 (mean ± SEM). In the presence of coronary artery constriction a similar decrease in EVR was observed and was accompanied by post-systolic shortening (PSS), an indicator of regional dysfunction. At high concentrations of halothane, there was an inverse correlation between reduction in EVR and increase in PSS. Mean EVR of approximately 0.9 (mean = 0.92 ± 0.02) was associated with significant worsening of regional function.

Endocardial viability ratio (EVR = diastolic pressure–time index:systolic pressure–time index) has been proposed as a reliable index of oxygen supply:demand ratio of the normal myocardium [1]. This index is used in patients with coronary artery disease [2], but there has been no study relating its reliability in the presence of a constricted coronary artery; an experimental model of constricted coronary artery could provide a means to assess this. Regional dysfunction of the canine myocardium has been shown to be a sensitive index of ischaemia in presence of coronary critical constriction and halothane anaesthesia [3]. This study was designed to compare EVR and regional myocardial dysfunction in the presence of compromised myocardial blood flow in dogs.

MATERIALS AND METHODS

Instrumentation

This study was performed in 13 mongrel dogs weighing 14–30 kg. The dogs were premedicated with morphine sulphate 0.3 mg kg^{-1} i.m. Anaesthesia was induced with thiopentone 15 mg kg^{-1} and the trachea intubated. Constant-volume intermittent positive-pressure ventilation was instituted at a rate of 12 b.p.m. and tidal volume 30 ml kg^{-1}, with a mixture of 70% oxygen in nitrogen to which sufficient carbon dioxide was added to maintain end-tidal carbon dioxide concentration at 5.3%. Anaesthesia was maintained during preparation with 0.7–1.5% inspired halothane supplied by a Fluotec vaporizer (Cyprane, Keighley, England) calibrated with a refractometer. In preliminary studies, we determined that this technique had the advantage of speeding up the attainment of stable alveolar anaesthetic concentrations and overcoming any tendency to develop atelectasis. Temperature was measured in mid-

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oesophagus and maintained between 37 and 38 °C by a heating element incorporated to the operating table.

The left common carotid artery was exposed and a rigid 7 French-gauge polyethylene catheter inserted and advanced to within 1 cm of the aortic valve for removal of blood samples and measurement of systemic arterial pressure via a Statham pressure transducer. An i.v. cannula was threaded via the femoral vein into the inferior vena cava for infusion of 0.9 % saline at a constant rate of 4 ml kg^{-1} h^{-1}.

A left thoracotomy was performed, the 5th and 6th ribs excised, and the heart exposed and suspended in a pericardial cradle. A rigid cannula was inserted in the left ventricle via a stab wound in the apical dimple and connected to a Statham pressure transducer.

The left anterior descending coronary artery (LAD) was dissected free distal to the second major diagonal branch. A 3-O woven Dacron suture was placed loosely about the artery and connected to a micrometer-controlled spring-suspended snare that could be tightened or loosened in increments of 2.5 µm. In six animals an electromagnetic flow probe (SEM 230 SE Laboratories) of appropriate diameter was placed around the vessel proximal to the snare and a pneumatic occluder was positioned distal to the probe to obtain zero flow readings.

Two pairs of ultrasonic piezoelectric crystals were placed in the subendocardium, at an angle of 90° to the long axis of the heart, using the technique previously described [3]. One pair was implanted in the area supplied by the LAD coronary artery distal to the isolated segment, the other in the area supplied by the left circumflex coronary artery (LC) to serve as a control segment.

Regional myocardial function

Regional myocardial function was assessed by obtaining continuous measurements of segment length between each pair of crystals, based upon measurement of ultrasonic transit times. A continuous analogue signal of dynamic segment length was provided by a repetitive stimulation rate of 1 kHz. The transit time was calibrated in steps of 1 µs generated by a quartz-controlled oscillator.

The signals were recorded on a Mingograf 81 eight-channel recorder (Elema Schonander, Stockholm, Solna, Sweden) at a paper speed of 100 mm s^{-1}. Figure 1 shows length tracings in relation to the haemodynamic variables recorded. End-diastole was defined as the time of onset of the sharp upslope of the first derivative of left ventricular pressure (LV dP/dt) signal, and end-systole as the dicrotic notch on the aortic pressure tracing.

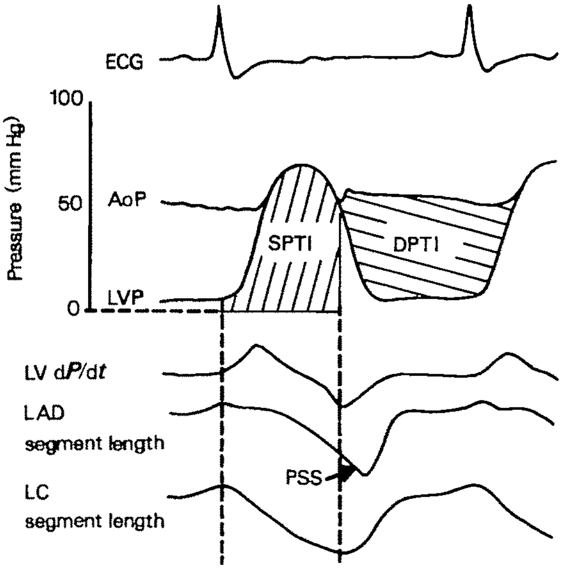

FIG. 1. Measurement of diastolic pressure–time index (DPTI) and systolic pressure–time index (SPTI) by planimetry in dog 1 with 2.0 % halothane concentration and critical constriction of the left anterior descending coronary artery. Note that post-systolic shortening (PSS) occurred in the ischaemic segment (LAD) but not in the non-ischaemic segment (LC). AoP = Aortic pressure. LVP = left ventricular pressure.

End-diastolic length (EDL), end-systolic length (ESL), maximum length during systole (SL_{max}), minimum length during systole (SL_{min}), and minimum length during diastole (DL_{min}) were obtained from the calibrated traces. The following formulae were used for derivatives of lengths:

Systolic shortening

$$\Delta SL = SL_{max} - SL_{min}$$
$$SL(\%) = (\Delta SL/SL_{max}) \times 100$$

Post-systolic shortening

$$PSS = ESL - DL_{min}$$
$$PSS(\%) = PSS/(SL_{max} - DL_{min})$$

Global haemodynamics

Arterial and left ventricular pressures were recorded. LV dP/dt was obtained by on-line differentiation. Heart rate was calculated from the R–R interval.

Diastolic pressure time index (DPTI) and systolic pressure time index (SPTI) were measured by planimetry, DPTI as the area under the curve between aortic and left ventricular pressures, and SPTI as the area under the ventricular pressure curve during systole [4] (fig. 1).

EVR was calculated as the ratio DPTI : SPTI in the same heart beat.

Procedure

After completion of the surgical preparation of the animal, a 1-h period of stabilization was allowed and the experiments were initiated at a minimum of 4 h after the administration of thiopentone.

Control recordings were obtained at a halothane concentration of 0.5–0.7 %. The inspired halothane concentration was increased subsequently in steps to 1.0 %, 1.5 % and finally 2.0 %. Each level of inspired halothane concentration was maintained for 10 min and recordings were obtained, since preliminary studies had demonstrated that circulatory stability was always achieved within 7 min. The halothane concentration was then returned to 0.5–0.7 %. All recordings were obtained during a 20-s period of apnoea at end-expiration.

A critical constriction of the LAD coronary artery was then imposed. In the first seven dogs the technique to obtain critical constriction was as previously reported [3]. Briefly, the snare was tightened by increments of 50 μm at 30-s intervals until changes indicative of ischaemia were observed in the LAD segment unaccompanied by such changes in the LC segment. The snare was then loosened by 50–100 μm until the ischaemic changes resolved. After a variable recovery interval, the micrometer was retightened by 12.5-μm increments until early changes of LAD contraction again occurred. The snare was then reloosened by 6.25 μm until these changes resolved, and a 20-min period allowed to elapse. A 90-s period of anoxia with 100 % nitrogen was then imposed. If ischaemic changes in LAD contraction occurred unaccompanied by similar changes in LC contraction, this degree of narrowing was considered a critical constriction. If not, further narrowing was imposed in 6.25–12.5 μm increments until a differential response to hypoxia was obtained.

In the last six dogs, constriction was applied in the same way, but was deemed to be critical if the degree of narrowing applied was such that 95 % of the normal hyperaemic response to a 10-s occlusion of the vessel was abolished. This method was used to avoid the systemic consequences of hypoxaemia. Coronary flow was used to establish the critical nature of constriction and was not measured later, thus avoiding repeated zero flow calibration occlusions which might disturb LAD segment function and exaggerate ischaemic dysfunction. These two methods of producing critical constriction demonstrated the same effects on global and regional myocardial function; thus these two sets of experiments were combined for statistical analysis.

Once a satisfactory and stable critical constriction had been obtained, and after a 20-min rest period, recordings were obtained as in the previous phase.

Statistics

The data were digitalized manually. Results were analysed for statistical significance using two-way analysis of variance followed by Duncan's multiple range test utilizing an SAS program—a commercially available statistical analysis program (SAS Institute, Cary, NC, U.S.A.). Chi-square test and linear regression were used when appropriate. $P < 0.05$ was considered significant. Results are expressed as mean ± SEM.

RESULTS

Global haemodynamics and EVR (table I)

Heart rate did not change significantly, whilst systolic arterial pressure, diastolic arterial pressure, DPTI, SPTI and EVR decreased significantly with increased halothane concentration, but the response was the same in the presence or absence of critical constriction.

Myocardial regional function (table I)

Before critical constriction, end-diastolic length increased and systolic shortening decreased significantly in both segments with increasing halothane concentrations.

With critical constriction of the LAD coronary artery, systolic shortening in the ischaemic segment was significantly more depressed at all but one halothane concentrations. However, the non-ischaemic segment (LC segment) was significantly less depressed than before constriction at 2.0 % halothane concentration.

TABLE I. *Haemodynamic and regional function effects (mean ± SEM) of increasing halothane concentration before and during constriction of the left anterior descending coronary artery in dogs ($n = 13$). Statistical significance (analysis of variance and Duncan's test): comparison with preconstriction or constriction control (0.5–0.7%): *P < 0.05, **P < 0.01; comparison with same inspired concentration preconstriction: †P < 0.05, ††P < 0.01*

	Before constriction				After constriction			
Halothane (%):	0.5–0.7	1.0	1.5	2.0	0.5–0.7	1.0	1.5	2.0
HR (beat min^{-1})	114.5±5.8	108.6±5.7	105.7±5.7	101.9±5.5	110.1±7.9	108.6±7.7	108.8±8.1	110.1±8.0
SAP (mm Hg)	102.5±3.0	89.7±3.1**	77.1±3.0**	60.9±3.4**	98.3±4.1	86.7±3.4**	76.3±4.1**	62.5±5.4**
DAP (mm Hg)	74.8±3.3	63 2±3.6**	52.1±3.3**	39.8±2.9**	70.8±4.5	60.5±3.0**	52.5±3.9**	42.0±3.7**
DPTI (mm Hg s)	26.0±1.2	22.2±1.0**	18.0±0.7**	13.4±0.8**	24.8±1.8	20.5±1.1**	17.6±1.5**	12.7±1.2**
SPTI (mm Hg s)	19.2±1.0	17.2±0.5*	15.2±0.5**	11.6±0.7**	19.0±0.9	17.2±0.7*	15.0±0.8**	12.0±1.1**
EVR	1.38±0.08	1.30±0.06	1.19±0.04**	1.15±0.04**	1.30±0.07	1.20±0.05*	1.16±0.05*	1.06±0.04**
LAD								
EDL (mm)	11.68±0.67	11.75±0.70	11.92±0.76	12.18±0.81**	11.51±0.59	11.65±0.62	11.89±0.68*	12.27±0.74**
ΔSL (%)	21.3±1.3	18.1±1.1**	15.3±1.1**	11.7±1.2**	19.0±1.5†	16.3±1.4*	12.1±1.4**††	7.5±1.0**††
PSS (%)	0.5±0.5	0.1±0.6	2.2±1.3	11.8±5.5*	4.5±2.6	7.8±3.3	26.2±9.9†	61.4±19.3**††
LC								
EDL (mm)	9.38±0.44	9.55±0.42	9.71±0.44**	9.90±0.43**	9.38±0.46	9.42±0.47	9.61±0.46*	9.89±0.46**
ΔSL (%)	14.7±1.4	13.7±1.1	11.8±1.1**	9 7±0.9**	13.2±1.3	11.6±1.1	10.5±0.9**	10.4±0.9**†
PSS (%)	6.8±6.1	7.0±4.6	11.7±5.5*	13.2±4.7*	10.1±5.1	18.1±10.3	25.7±9.6**†	23.1±10.6

TABLE II. *Number of observations according to the value of endocardial viability ratio (EVR) and the presence of post-systolic shortening in ischaemic LAD segment (PSS)* (n = *56*, χ^2 = *9.87, df. = 1, P < 0.01)*

	EVR < 1.25	EVR ⩾ 1.25
No PSS	14	14
PSS present	20	4

PSS in the LC segment was significant at the two higher halothane concentrations, but was less than 0.2 mm both before and after critical constriction. PSS in the LAD segment was small before constriction. In the LAD segment, with critical constriction, PSS up to 61.4%±19.3 of total systolic shortening occurred at a halothane concentration of 2.0%.

Comparison of EVR and myocardial regional function

PSS was more common when EVR was less than 1.25 ($P < 0.01$) (table II). As there was essentially no PSS in the ischaemic LAD segment

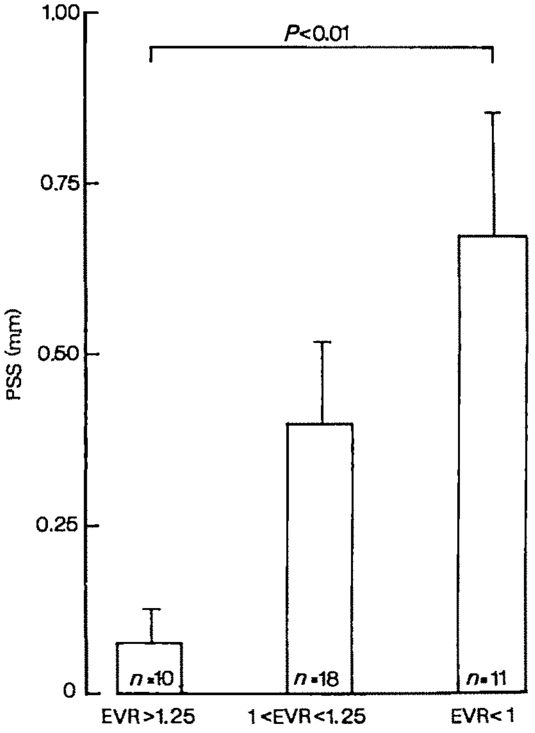

FIG. 2. Comparison of post-systolic shortening (PSS), according to the value of endocardial viability ratio (EVR) (mean ± SEM) at the three higher halothane concentrations. *P* value refers to unpaired Student's *t* test.

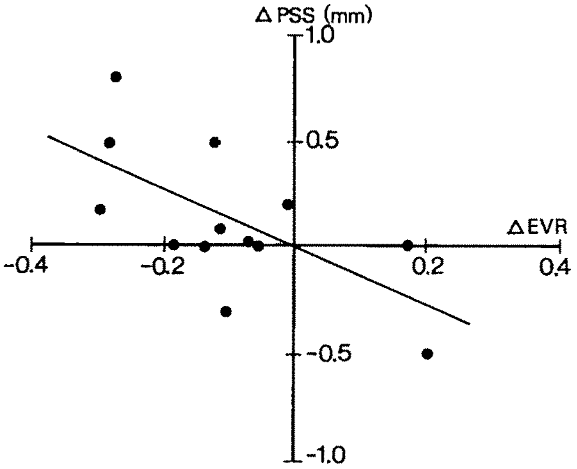

FIG. 3. Correlation between the changes in post-systolic shortening (PSS) and in endocardial viability ratio (EVR) when halothane concentration was increased from 1.5 to 2.0% (r = 0.65, slope = −1.35, $P < 0.02$).

with the lowest halothane concentration, we compared values of PSS in the three higher halothane concentrations based upon the values of EVR. PSS was lower when EVR was greater than 1.25:0.08 ± 0.04 mm, compared with 0.50 ± 0.10 mm ($P < 0.025$) for EVR less than 1.25. This difference in PSS increased when comparing the extreme values of EVR (fig. 2). Similarly, EVR was greater (1.21 ± 0.04) when PSS was absent than when it was present (1.08 ± 0.04) ($P < 0.025$).

When individual EVR and PSS values in the LAD ischaemic segment were correlated, there was a significant negative linear correlation ($r = -0.41$, slope = -0.89 ± 0.28, $n = 52$, $P < 0.01$). Moreover, when halothane concentration was increased from 1.5 to 2.0%, there was a correlation between increase in PSS and decrease in EVR ($r = -0.65$, slope = -1.35 ± 0.48, $n = 13$, $P < 0.02$) (fig. 3); the regression line passed through the origin of the axes.

Several haemodynamic parameters, including the rate–pressure product (HR × SAP), were compared when EVR was less than or equal to 1.00 and greater than 1.25 (table III). These parameters were not significantly different in the two sets, but the lower values of EVR were associated with significantly lower SPTI ($P < 0.05$) and DPTI ($P < 0.001$). Despite the significant difference in DPTI, there was no correlation between reduction in DPTI and PSS. There was also no correlation between EVR and systolic shortening.

TABLE III. *Comparison of haemodynamic parameters (mean ± SEM) at the three higher halothane concentrations and in the presence of critical constriction of the LAD coronary artery, when EVR is less than or equal to 1 and larger than 1.25. Statistical significance (unpaired Student's* t *test):* *P < *0.05;* **P < *0.001*

	EVR > 1.25 (n = 10)		EVR ⩽ 1 (n = 11)
EVR	1.36 ± 0.02	**	0.92 ± 0.02
HR (beat min^{-1})	90.6 ± 7.6		110.4 ± 6.1
SAP (mm Hg)	74.7 ± 2.9		66.8 ± 6.3
DAP (mm Hg)	51.2 ± 3.4		44.8 ± 4.4
LVEDP (mm Hg)	5.1 ± 0.6		6.9 ± 0.9
CPP (mm Hg)	46.1 ± 3.5		37.9 ± 4.4
RPP (mm Hg min^{-1})	6830 ± 760		7615 ± 1075
DPTI (mm Hg s)	22.4 ± 1.2	**	12.1 ± 1.2
SPTI (mm Hg s)	16.4 ± 0.88	*	13.2 ± 1.2

DISCUSSION

Determination of EVR has been suggested as a method to monitor ischaemia of the inner layers of the myocardium which are particularly susceptible to ischaemia [5]. In their original study, Buckberg and co-workers [6] observed that the inner:outer myocardial flow ratio began to decrease when the DPTI:SPTI ratio decreased below a range of 0.5–0.8. Griggs and Chen [7] showed, in dogs with experimental aortic incompetence, that the subendocardial lactate:pyruvate ratio began to increase when aortic and left ventricular pressures gave a ratio equivalent to a DPTI:SPTI ratio of 0.4. In healthy men studied by Barnard and co-workers [8], ST depression on sudden maximal exercise was not seen until EVR was less than 0.45, and no ST changes were seen with EVR greater than this value. Thus Hoffman and Buckberg [1] suggested that a more correct figure to choose for the critical value below which the inter:outer flow ratio begins to decrease is 0.4–0.5. However, in 35 patients, Philips and co-workers [9] showed that, in the early period after cardiopulmonary by-pass for correction of valvular or coronary artery disease, EVR had prognostic value: when EVR was less than 0.7, the patients needed cardiac assistance using intra-aortic balloon counterpulsation, and the five patients with EVR less than 0.55 died. There is no experimental study relating the reliability of EVR in presence of critical coronary constriction and anaesthesia.

PSS has been observed to be a marker of regional ischaemia [3]. Reductions in systolic shortening and systolic thickening have also been utilized as markers of regional function and ischaemia by various groups [10–13]. However, all of these investigators used a model utilizing a constant level of anaesthesia and thus a constant degree of myocardial depression. In this study, as in that of Lowenstein and colleagues [3], the anaesthetic depth was varied in order to examine its effects on compromised myocardium and regional myocardial function. As seen during the control period when coronary arteries are undisturbed, increases in halothane concentration cause myocardial depression and thus decrease systolic shortening and, by inference, systolic thickening. However, as Lowenstein's group [3] observed, it is only after critical constriction had been applied that substantial PSS occurred in response to deepening halothane anaesthesia and was far more suggestive of ischaemic dysfunction than the significant but relatively modest worsening of regional shortening. Therefore, in the context of varying depth of anaesthesia, PSS is a more sensitive indicator of myocardial ischaemia than is the reduction of systolic shortening. PSS may occur when the excitation–contraction coupling is disturbed by other interventions such as exposure to the combined effect of verapamil and halogenated anaesthetics [14, 15] or the addition of nitrous oxide to halothane [16]. However, none of these combinations was used in the present study.

Using PSS as a marker of ischaemia, it can be seen that EVR less than 1.0 was associated with a large amount of PSS while EVR greater than 1.25 was associated with little or no PSS (fig. 2). An EVR of greater than 1.25 is seldom associated with PSS (table II). However, an EVR of less than 1.0 appears to be a good predictor of ischaemia in the presence of critical coronary artery stenosis. The significant inverse correlations between PSS and EVR ($r = 0.41$, $P < 0.01$) and between changes in EVR and changes in PSS at high halothane concentrations ($r = -0.65$, $P < 0.02$) (fig. 3) confirm the predictive value of EVR for myocardial ischaemia.

The critical value of EVR appears to be much greater than previously proposed values of 0.4 and 0.7 [7, 9]. This may not be surprising. Whilst Sarnoff and colleagues [17] showed a close relationship between the tension–time index (SPTI) and myocardial oxygen consumption in a canine model, others showed that this index only predicts myocardial oxygen consumption with wide individual variability [18], because changes in contractility and ventricular dimensions are not correctly reflected. In the current study, SPTI may have correlated poorly with oxygen consumption because contractility decreased and end-diastolic dimensions increased. Indeed, the 21% decrease of SPTI on increasing the halothane concentration from 0.5% to 1.5% is smaller than the 26% decrease of myocardial oxygen consumption observed by Smith and colleagues [19]. However, the 31% decrease in coronary blood flow observed by these authors is similar to the decrease of DPTI before critical constriction in the present study.

However, critical constriction reduces coronary blood flow by approximately 20% and makes it proportional to the driving pressure [20]. Since critical constriction is not accompanied by significant haemodynamic alterations, DPTI remains unchanged and overestimates oxygen supply. Moreover, the values of DPTI are comparable only for the same impairment of the coronary arteries and the same oxygen content of arterial blood [4]. The overestimation of DPTI is probably more important than the overestimation of SPTI. If DPTI overestimates oxygen supply in the presence of coronary artery stenosis, the critical value for EVR is bound to be higher for the compromised heart than for the normal heart. It is therefore not surprising that the critical value of EVR (0.92 ± 0.02) was found to be much higher than previously reported.

In our study, EVR was calculated by planimetry, but EVR can be monitored if peripheral

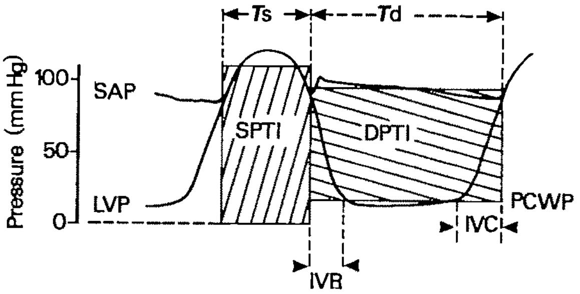

FIG. 4. DPTI and SPTI as calculated by Philips' formula [9]. Note that DPTI is overestimated and SPTI underestimated, as compared with measurement by planimetry. IVR = isovolumic ventricular relaxation; IVC = isovolumic ventricular contraction; *Ts* and *Td* = duration of systole and diastole, respectively, as available in absence of recording of left ventricular pressure; LVP = left ventricular pressure, SAP = systemic arterial pressure; PCWP = pulmonary capillary wedge pressure which approximates left ventricular end-diastolic pressure.

arterial and pulmonary capillary wedge pressures are measured (fig. 4) instead of aortic and left ventricular pressures [9, 21]. The following formula can be used:

$$\mathrm{EVR} = \frac{\mathrm{DPTI}}{\mathrm{SPTI}} = \frac{(\mathrm{DP}-\mathrm{PCWP}) \times Td}{\mathrm{SP} \times Ts}$$

where DP = mean systemic diastolic pressure; PCWP = pulmonary capillary wedge pressure; SP = mean systemic arterial pressure; Td = diastolic time; Ts = systolic time.

A commercially available computer can be used to calculate the EVR from the arterial and pulmonary artery pressures on a beat-by-beat basis using the above formula [21].

Using planimetry for EVR calculation introduces a difference between our experimental EVR measurement and estimation of EVR clinically. If the measurement of SPTI is compared in Philips' formula [9] and in our measurements, the area under the ventricular pressure curve during isovolumic ventricular contraction (approximately 7% of SPTI) is not taken into account by Philips' formula (fig. 4). This area is included in the measurement of DPTI in Philips' formula, in addition to the area under the ventricular pressure curve during isovolumic relaxation, and thus DPTI is overestimated by approximately 10%. As a result, the critical value of EVR estimated by Philips' formula should be almost 18% larger than our reported value,—approximately 1.08.

This study demonstrates an inverse relationship between EVR and regional myocardial dysfunction (PSS) in an area supplied by a critically constricted coronary artery, and shows that the critical value of EVR (0.96) is markedly higher than previously proposed and that EVR is a better indicator of ischaemia than conventional haemodynamics or rate–pressure product, both of which failed to predict the occurrence of EVR equal to or less than 1.0 (table III). If EVR is used to assess subendocardial viability, values of approximately 1.0–1.25 should be considered as the threshold for ischaemia in the presence of a critically stenosed coronary artery. However, as pointed out by Kaplan [21], the critical value of EVR cannot be predicted in patients with various degrees of coronary disease, and the changes in EVR may prove useful in assessing the adequacy of the oxygen balance in a given patient. Because EVR is easier to obtain than any measurement of regional wall motion, it may prove a valuable indicator of subendocardial ischaemia once it is accepted that the threshold value is much higher than previously reported.

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MEASUREMENT OF ARTERIAL PRESSURE USING CATHETER–TRANSDUCER SYSTEMS

Improvement Using the Accudynamic

M. W. B. ALLAN, W. M. GRAY AND A. J. ASBURY

SUMMARY

The dynamic performance of arterial manometers depends upon the values of the natural frequency f_0 and the damping factor β. Satisfactory reproduction of all arterial waveforms requires that f_0 should be greater than about 13 Hz; for an f_0 of 13 Hz, β should have a value of 0.5, but, as f_0 increases, an increasing range of β values is permissible. We measured f_0 and β for two pressure transducers (Gould P23 Statham and Gould Disposable) in combination with Portex or Gould catheter tubing of lengths varying from 100 cm to 300 cm. All combinations were considerably underdamped, with the best having an f_0 of 30 Hz and a β of 0.1. We also investigated the performance of a commerical device, the Accudynamic, designed to allow β to be increased without affecting f_0. We found that the Accudynamic worked well, allowing acceptable performance to be obtained from the Gould Disposable transducer with catheters up to 200 cm in length.

Since Frank's (1903) [1] original analysis of the behaviour of arterial manometers various theoretical and practical studies have been published. If certain simplifying assumptions are made, it can be shown that arterial manometers behave like "second order dynamic systems" [2, 3]. Their performance can then be quantified in terms of three parameters—the natural frequency f_0, the damping factor β, and the static sensitivity K—the values of which are determined by the physical properties of the system [4, 5]. These quantitative relationships are summarized in the Appendix, which contains a fuller discussion of the theoretical analysis of manometer behaviour.

Satisfactory performance of an arterial manometer can be obtained only if f_0 and β have suitable values. Gardner [6] has presented the range of acceptable values for f_0 and β in the graphical form reproduced in figures 4–6. It can be seen that, for a normal arterial waveform, the lowest acceptable f_0 is 7 Hz and the corresponding value of β is about 0.5; as f_0 increases, a progressively increasing range of values of β is acceptable. For a demanding waveform, the shape of the acceptable region of f_0 and β values is similar, but the region is shifted towards higher values of f_0, so that the lowest acceptable value is 13 Hz. As the Appendix shows, high values for f_0 can be achieved with a stiff transducer diaphragm and a short, wide catheter; however, attempts to increase f_0 by manipulating the physical properties of the system usually have the undesirable effect of decreasing β. Conversely, an increase in β is achieved at the expense of a decrease in f_0.

Previous investigators have shown that manometer systems in clinical use are usually underdamped [6, 7]. The purpose of this study was to examine the dynamic performance of typical catheter–transducer systems, and to investigate the performance of the Accudynamic—a commercially available device for increasing β without altering f_0.

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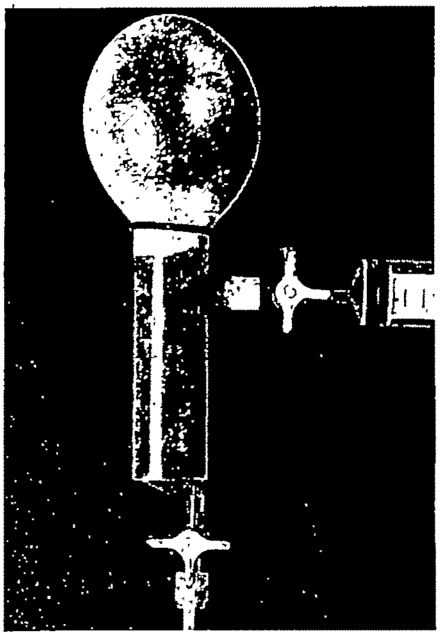

FIG. 1. Apparatus used for transient testing.

MATERIALS AND METHODS

Transient test

We studied two pressure transducers, the Gould P23 Statham with disposable dome, and the Gould Disposable. Both have integral flushing devices. Two different makes of catheter were studied, Gould and Portex. The Gould catheter is available in a length of 150 cm and its internal diameter is 2 mm, while the Portex catheter is available in 60, 100, 150, 200 and 300 cm lengths and has an internal diameter of 1.5 mm. The following tests were carried out with each transducer connected in turn to 150 cm and 300 cm of Gould tubing (two 150-cm lengths connected together), and to 100 cm, 200 cm and 300 cm of Portex tubing.

Natural frequencies and damping factors were calculated from the results of a transient "pop" test [8] using the apparatus shown in figure 1. A finger cut from a surgical rubber glove was drawn across the end of the barrel of a 20-ml plastic syringe (with its flange cut off) and held in position by a rubber O-ring. The syringe was half filled with saline, and connected to the transducer under test via the catheter being studied. A three-way tap was attached to a male Luer connector fixed into the side of the barrel and secured by a nut. The whole apparatus was fixed to a drip stand. After inflation with a 50-ml syringe via the side arm, the balloon was burst with a hot soldering iron.

The transducer under test was connected to a Simonsen and Weel 8000 pressure amplifier, the signal from which was displayed on a Simonsen and Weel Triscope and also on an Elema–Schonander ink-jet recorder with the paper speed set to 500 mm s^{-1}. Each series of tests on a given transducer model was carried out on a sample of five transducers. The system was flushed and recalibrated before each test. The f_0 and β of each system were calculated as described by Gabe [8] using the measurements shown in figure 2. (It was not necessary to measure the static sensitivity, K, which is purely a scaling factor and is automatically evaluated when the pressure measurement system is calibarated.)

Accudynamic

The Accudynamic (Sorensen Research Co.) is a recently introduced device intended to allow β to be increased without affecting f_0 (fig. 3). The side arm contains an air bubble of about 0.1 ml which

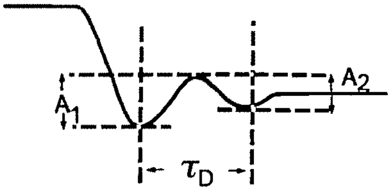

FIG. 2. Typical result of transient test. β is obtained from A_2/A_1 and f_0 for τ_D and β, as described by Gabe [8].

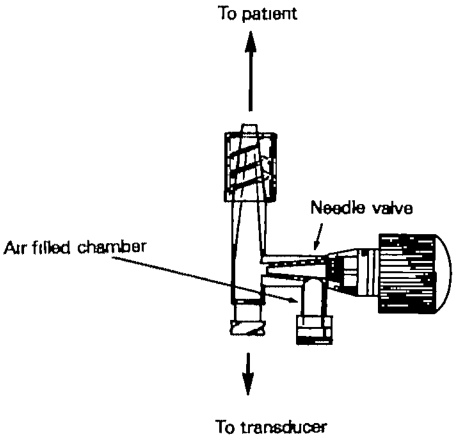

FIG. 3. Accudynamic. The resistance of the passage leading to the air buddle depends on the setting of the needle valve, which is adjusted by the control knob.

is linked to the liquid in the catheter–transducer system through a narrow channel containing physiological saline. The effective cross-sectional area, and therefore the resistance, of this channel can be varied by adjustment of the needle valve. The device effectively acts as a variable fluid resistance in parallel with the compliance of the transducer. Correct adjustment of the resistance allows pressure waves travelling down the catheter from the patient to be dissipated in the resistance and so reduces reflections and the constructive interference of primary and reflected waves that gives rise to resonance. The principle of the device is discussed further in the Appendix. Its performance has been described by Gardner [6], who found that it operated satisfactorily.

Tests on a Gould Disposable transducer and 200-cm Portex tubing or 150-cm Gould tubing were performed with an Accudynamic connected between the catheter and the transducer. f_0 and β were measured with the control knob fully closed and then with it opened in quarter-turn increments until it had been rotated through one full turn.

RESULTS

When care was taken to ensure that no air bubbles were present in the system, the values obtained for f_0 and β for different samples of the same transducer with the same catheter configuration were very consistent, with the coefficients of variation being less than 0.2 % and 0.75 % for f_0 and β, respectively. Figures 4 and 5 show the variation in f_0 and β as the length of catheter tubing was increased. The best combination appeared to be Portex catheter tubing with the Gould Disposable transducer, although it was not possible with any of the systems tested to achieve values of f_0 and β within the range which Gardner [6] considered acceptable for demanding pressure waveforms. Figure 6 illustrates the increase in β achieved with the Accudynamic as the control knob was rotated from the fully closed position. At one full turn, calculation of β was not possible with the pop test method because there were

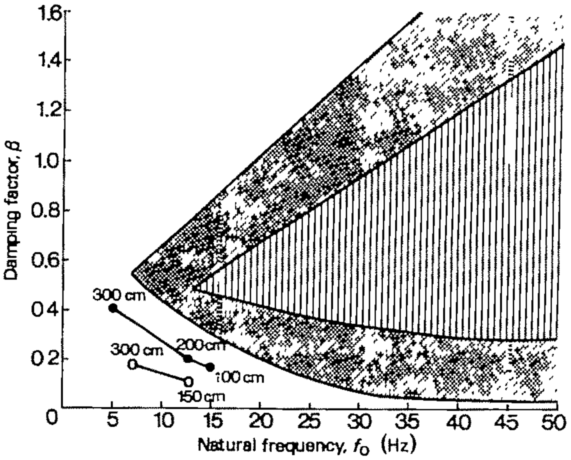

FIG. 4. Results for Gould P23 transducer. ●——● = Portex catheter. ○——○ = Gould catheter. Gardner's [6] acceptable regions for a demanding and for a normal pressure waveform are indicated by the inner and outer shaded areas, respectively.

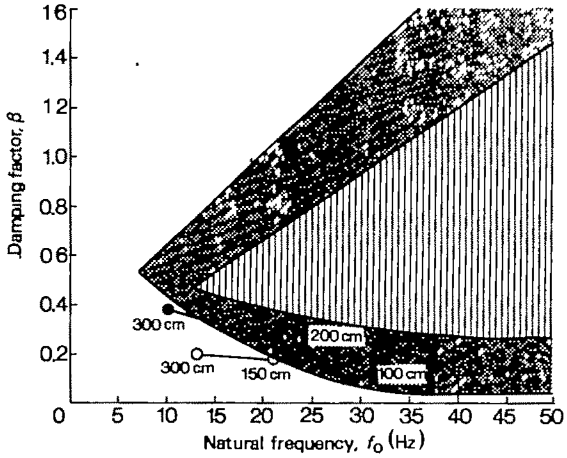

FIG. 5. Results for Gould Disposable transducer. Symbols and shaded areas as in figure 4.

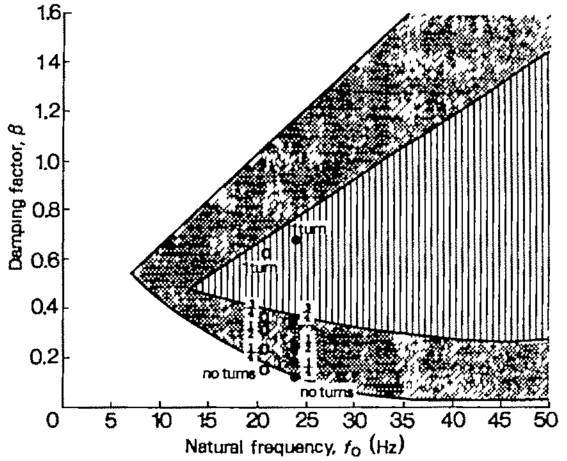

FIG. 6. Effect of adjusting Accudynamic control on dynamic response of Gould Disposable transducer when used with Portex 200-cm catheter (●) or Gould 150-cm catheter (○) Shaded areas as in figure 4.

insufficient oscillations. However, by comparison of the recorded waveform with transient response curves for a second-order instrument [5], it was estimated that β had a value between about 0.6 and 0.7. It can be seen from figure 6 that the use of the Accudynamic allowed β to be increased without reducing f_0, and enabled the performance of the system to be brought into Gardner's acceptable range for a demanding waveform.

DISCUSSION

If an arterial pressure measurement system has very low damping ($\beta \ll 1$), then the recorded waveform will tend to be distorted because of the uneven response of the system to the different component frequencies of the pressure waveform (fig. 7). This distortion can be avoided by arranging for f_0 to be much higher than the highest frequency in the pressure waveform, and this is the rationale for the use of catheter-tip transducers [9]. However, for conventional catheter–transducer systems, sufficiently high f_0 cannot be achieved; as these systems are generally underdamped [6, 7], extra damping must be introduced to minimize the distorting effects of the measurement system's tendency to resonate. Figure 7, which is discussed more fully in the Appendix, illustrates the effects of different degrees of damping on the system's behaviour.

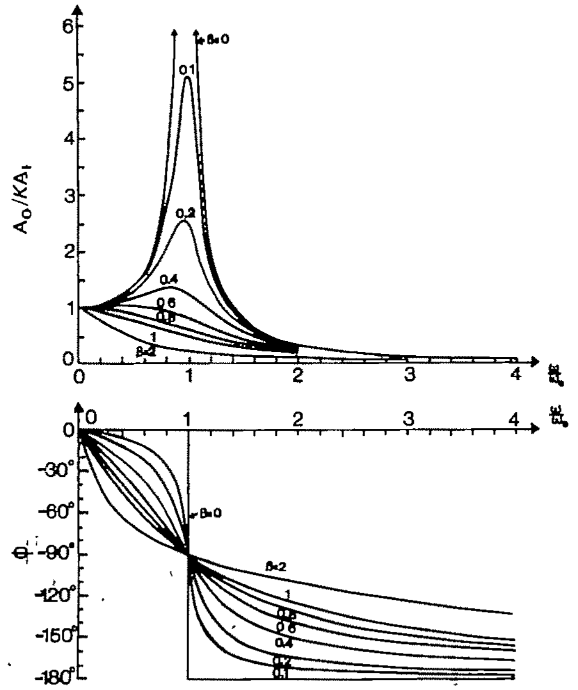

FIG. 7. Frequency response curves for a second order instrument. A_i and A_0 are the amplitudes of the input and output signals, respectively; K is the static sensitivity and φ is the phase difference between the output and input; negative values of φ indicate a phase lag. (adapted from Doebelin [5].)

Gardner's criteria for acceptable values for f_0 and β, shown in figures 4–6, were obtained from a computer simulation of the effects of adjusting f_0 and β on two arterial pressure waveforms—a typical waveform and a demanding waveform. A demanding waveform is one consisting of a rapid upstroke of the arterial pressure trace (i.e. a high dP/dt), especially in the presence of a rapid heart rate. Our results support previous findings that commonly used catheter–transducer systems are underdamped [6, 7], and only with the Gould Disposable transducer connected to 100 cm or 200 cm of Portex tubing did we achieve acceptable values of f_0 and β for Gardner's less demanding waveform. Underdamped systems can lead to overestimation of systolic pressures by up to 30 mm Hg and underestimation of diastolic pressures by a similar amount, although the mean pressure recorded will be accurate [6, 8]. The consequences of a clinical decision being made on the basis of erroneous readings such as these could be undesirable.

Our experience indicates that the Accudynamic lives up to its manufacturer's claim of allowing β to be increased without reducing f_0. To help achieve the appropriate setting in clinical practice, the manufacturers recommend assessing the degree of damping by a variation of the transient "pop" test, in which a pressure transient, produced by the opening and quick release of a fast flush device, is observed on an oscilloscope screen. The Accudynamic is then adjusted and the procedure repeated until the resulting waveform appears to have optimal damping. We have found this a satisfactory technique, and it has the advantage of testing the whole system whilst attached to the patient. However, interpretation of the waveform does require some experience. The use of the Accudynamic allows faithful reproduction of arterial waveforms provided that the value of f_0 for the catheter–transducer system is greater than about 15 Hz. This requirement will be met only if excessively long or compliant catheter tubing is avoided, and if scrupulous attention is paid to flushing out all air bubbles from the system [8].

Since catheter–transducer systems are becoming more widely used in clinical practice, it is important that clinicians are aware of their characteristics, the criteria for their assessment, and the methods for optimizing their performance. Ideally, all catheter–transducer systems should have f_0 and β estimated before use, and action be taken to adjust β if necessary. It is encouraging to note that, in more recent papers [10, 11], values for f_0 and β were stated for the arterial pressure measurement system used, and appropriate action taken to ensure high fidelity reproduction.

APPENDIX

DYNAMIC BEHAVIOUR OF MANOMETERS

An arterial manometer is a measurement system [5] in which the input variable is arterial pressure and the output variable is the volume displacement of the transducer diaphragm. In considering the dynamic behaviour of manometers, we are attempting to elucidate the input–output relations of this particular measurement system and, in particular, to examine how they depend on the physical characteristics of the system.

Manometer as a single degree of freedom system

In the simplest analysis of manometer behaviour, the compliance of the manometer tubing and the compressibility of the manometer liquid are neglected, and the liquid is considered to move as a single mass, so that the volume displacement at any given time is the same at all points in the system. The system can thus be described by a single coordinate at a given time and is known as a *single degree of freedom system* [12]. Mathematical analysis of the input–output relations leads to a linear second order differential equation and the arterial manometer is therefore classed as a *second-order instrument* [5]. The performance of a second-order instrument depends on three parameters, which are related to the physical properties of the system; these are the static sensitivity, K, the undamped natural frequency, ω_0 and the damping factor, β. ω_0 is an angular frequency, measured in radians per unit time, and is equal to $f_0/2\pi$, where f_0 is measured in cycles per unit time. If the assumption is made that the resistance to flow in the manometer system can be described by Poiseuille's equations, then the following relations hold [4]:

$$K = 1/E \tag{1}$$

$$\omega_0 = r\sqrt{\frac{\pi E}{\rho L}} \tag{2}$$

and

$$\beta = \frac{4\mu}{r^3}\sqrt{\frac{L}{\pi\rho E}} \tag{3}$$

where E is the volume elasticity of the transducer diaphragm $(\Delta P/\Delta V)$; r is the radius of the manometer tubing; L is the length of the manometer tubing; ρ is the density of the manometer liquid; and μ is the viscosity of the manometer liquid. Note that the static sensitivity, K, is equal to the compliance of the transducer diaphragm $(1/E)$.

The performance of a second-order system depends on the frequency content of the input waveform in addition to the values of K, ω_0 and β; the dependence of the output:input amplitude ratio and phase difference upon the input frequency is known as the *frequency response* of the instrument. Frequency response curves for a second-order instrument are shown in figure 7. When $\beta < 1$, the system is said to be underdamped, and this condition normally holds for arterial manometer systems [6, 7]. The frequency response curves show that, for $\beta < 1$, the phenomenon of resonance occurs. the amplitude ratio increases from a value of K when $\omega = 0$ to a maximum value when ω is close to ω_0, with the maximum value being greater the smaller the value of β. The range of ω for which the amplitude response remains reasonably flat depends upon the value of β: McDonald [9] stated that the optimum value for β is 0.64, at which value the amplitude ratio remains flat to within 2 % for ω up to 67 % of ω_0, and the input–output phase lag increases almost linearly with ω up to ω_0. (This latter characteristic is desirable, since it implies that the output waveform will not suffer from phase distortion of its components.)

As indicated earlier, the above analysis involves the assumption that the resistance to flow can be described by Poiseuille's equation. If this assumption is not valid, then the expression obtained for β will be incorrect (equation (3)). In fact, since Poiseuille's equation applies only to steady laminar flow, it is not strictly applicable to the motion of manometer liquid, which is oscillatory in nature. For oscillatory flow, the resistance is higher than predicted by Poiseuille's equation and increases with the frequency of the oscillation [9]. Consequently, the effective value of β is greater than predicted by equation (3). However, a more exact analysis is complex, and most authors assume Poiseuille resistance when analysing manometer behaviour. Indeed, as McDonald [9] showed, the improvement in prediction produced by a more exact analysis is marginal. For our purposes, the simplified analysis summarized above is adequate for indicating the relationships between the physical properties and the dynamic behaviour of a manometer system and for leading on to the treatment of a manometer as a distributed system.

Manometer as a distributed system

The assumptions involved in treating a manometer system as a single degree of freedom system (incompressible liquid and rigid tubing) imply that any change in arterial pressure will be transmitted instantaneously to the transducer diaphragm, that is, the pressure wave is propagated at infinite speed. In reality, the manometer liquid is not incompressible and the tubing not completely rigid, and an input waveform travels with finite speed down the manometer tubing. The volume displacement is now not identical at all points in the system at a given time; in fact, it can vary continuously along the system which, therefore, has effectively infinite degrees of freedom [12]. Such a system is known as a *distributed system*.

The propagation of pressure waves along a manometer system is analogous to the propagation of electromagnetic waves along a transmission line, and the theoretical behaviour of the manometer can be derived from transmission line theory, if the electromagnetic variables are replaced by the analogous hydraulic variables [2, 3, 8, 13]. One of the important conclusions is that, in general, a pressure wave travelling down a manometer line will be partially reflected at the transducer and travel back to the artery, where it will again undergo reflection and travel back towards the transducer. Resonance occurs as the result of constructive interference of the direct and reflected waves at the transducer. As the elastic moduli of the manometer liquid and the tubing material become very large, the behaviour of the system becomes identical to that of a single degree of freedom system [2, 3]

The reflection of pressure waves at the transducer does not occur if the total hydraulic impedance presented to the manometer line is equal to the *characteristic impedance* of the line. Instead, the wave is dissipated in the terminating impedance. Since the value of the transducer impedance is about 100 times larger than the characteristic impedence for frequencies up to 20 Hz, for the types of transducer and catheter used in the present study, the line is effectively terminated by an obstruction [8], and the wave will be totally reflected unless preventive measures are taken. Van der Tweel [13] pointed out that the reflections could be reduced or avoided if a resistive element with resistance equal to the characteristic impedance of the catheter were installed in parallel with the transducer. The Accudynamic is designed to allow this impedance matching to be accomplished.

PRINCIPLE OF ACCUDYNAMIC

In the Accudynamic (fig. 3) the needle valve constitutes a variable resistance and the 0.1-ml air bubble effectively acts as a compliance that couples the resistive element to atmospheric pressure for cyclic pressure changes, but blocks the passage of steady signals and thus prevents loss of liquid from the system. Thus for the varying components of the arterial waveform, the device acts as a variable resistance in parallel with the transducer; it therefore allows the impedance presented to a pressure wave to be adjusted to match the characteristic impedance of the catheter system.

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CONTROLLED COMPARISON OF A NEW SUBLINGUAL LORMETAZEPAM FORMULATION AND I.V. DIAZEPAM IN OUTPATIENT MINOR ORAL SURGERY

C. A. O'BOYLE, H. BARRY, E. FOX, C. McCREARY AND A. BEWLEY

SUMMARY

In a randomized, double-blind, parallel groups study, 40 patients undergoing surgical removal of impacted 3rd molar teeth received either sublingual lormetazepam 2.5 mg (n = 20) in a new cellulose wafer formulation followed at 35 min by i.v. saline; or sublingual placebo followed at 35 min by i.v. diazepam 10 mg (Diazemuls). Rapid onset of sedation was seen after sublingual lormetazepam, while the course and duration of postoperative sedation, measured using standard psychometric tests, was similar following both treatments. Surgeons' ratings indicated that sublingual lormetazepam was comparable to i.v. diazepam but patients' ratings indicated greater satisfaction with and preference for i.v. diazepam. Significant anterograde amnesia was found following both treatments. Both treatments were tolerated well, with no significant cardiovascular complications. These results indicate that sublingual lormetazepam may have a role in anaesthesia as a premedicant and for conscious sedation.

Although i.v. benzodiazepine sedation has become a well established technique for ambulatory outpatient procedures, there are a number of hazards associated with the i.v. route [1, 2]. Oral sedation, using new, rapidly-acting benzodiazepines has been shown to provide a viable alternative to the i.v. technique for such procedures [3, 4].

Lormetazepam is a benzodiazepine which is devoid of active metabolites and is characterized by rapid absorption and a terminal plasma half-life of approximately 10 h following oral administration [5]. In an attempt to increase further the absorption rate of lormetazepam, a novel formulation of the drug has been designed for sublingual administration [6]. This consists of a small square wafer (12 mm × 12 mm) composed of lormetazepam 1 mg as a solid solution in a cellulose carrier. The cellulose wafer is odourless and tasteless and dissolves rapidly when administered sublingually. Plasma lormetazepam concentrations are significantly higher between 7.5 and 25 min following sublingual wafer administration than after conventional oral tablet administration [6]. In an open pilot study, in gastroendoscopy, using 1.5, 2 or 2.5 mg doses of lormetazepam in the new formulation, we found dose-related sedation with good operating conditions, especially at the higher doses (unpublished data). The response was somewhat variable and the data indicated the need for a placebo-controlled trial of the drug. The present study was designed to assess sublingual lormetazepam in a test situation previously found to be sensitive to the sedative and anxiolytic effects of benzodiazepine drugs [3, 4].

PATIENTS AND METHODS

Forty healthy adult outpatients who were judged to require sedation for removal of impacted 3rd molar teeth gave informed written consent to the study, which was approved by the hospital Ethics Committee. Selection and exclusion criteria were the same as in previous studies [3, 4].

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The experimental design and schedule of assessments were identical to those used previously [4]. Patients were allocated randomly to treatment conditions by means of a random number table. Group I ($n = 20$) received sublingual lormetazepam 2.5 mg (Noctamid, Schering Ag. Ltd) in the cellulose wafer formulation 35 min before receiving saline 2 ml i.v. 5 min before the start of the procedure. Patients were instructed to place the wafer under the tongue, away from the back of the teeth, and to refrain from speaking until the wafer had dissolved completely. Group II ($n = 20$) received matching sublingual placebo followed, at 35 min, by diazepam 10 mg i.v. (Diazemuls), titrated at a rate of 2.5 mg per 30 s. The study was double-blind from the point of view of the surgeon and the psychologist but, because of the dissimilarity in appearance between Diazemuls and placebo, the anaesthetist was aware of the treatment given to each patient. The anaesthetist was not involved in any of the assessments, and all drugs were administered in the absence of the surgeons and psychologist.

Following the i.v. infusion, the appropriate dental anaesthetic block was performed using 2% lignocaine and 1:80000 adrenaline. A standard surgical procedure was adopted which consisted of removal of impacted 3rd molars under inferior dental block. Verbal contact was maintained with the patients throughout surgery. Postoperative management was identical to that reported previously. The following week patients returned for suture removal and memory assessment.

Assessments

Detailed descriptions of assessment techniques and the timing of assessments are published elsewhere [4].

Briefly, trait anxiety for dental procedures was assessed by means of the Corah Dental Anxiety Scale [7], while preoperative and postoperative levels of state anxiety were assessed using the state scale of the Spielberger State Anxiety Inventory (STAI) [8]. Visual analogue scales (VAS) (100 mm) measuring anxiety and tension were also used. The onset of impairment in psychomotor function and subsequent recovery of normal function were measured by means of the digit–symbol substitution test (DSST). VAS measuring drowsiness, mental slowness and clumsiness were also administered. Amnesia was assessed by means of a visual memory test (VMT) and a memory questionnaire [9]. The VMT involved showing photographs before and after sedation and testing subsequent recall at 1 week. The memory questionnaire assessed memory for a number of actual surgical events (e.g. drilling, extraction of tooth). Systolic (SAP) and diastolic (DAP) arterial pressure and heart rate (HR) were monitored (Dinamap 847 automatic monitor).

Immediately after surgery, both surgeons independently rated intraoperative anxiety, cooperation, relaxation, ease of access, degree of swallowing, ptosis, phonation and hand/arm movement on a series of 100 mm VAS. Global impression of the sedation ("good", "satisfactory" or "poor") was also rated by both surgeons. Patients rated their satisfaction with sedation, opinion of the operation and future sedation preference on their return visit at 1 week. At this time, patients also rated the extent to which they felt normal, confused, sick and in pain on the evening of surgery.

RESULTS

The treatment groups were comparable in age, sex, weight and height (table I). Preoperative levels of state and trait anxiety and psychomotor performance (DSST), and scores on the VAS were also comparable. One patient who had indicated previously that she was not taking any psychotropic medication subsequently admitted to having taken benzodiazepines the night before surgery. This patient, who had been given lormetazepam, was eliminated from the study. Two patients in each group failed to return for follow-up assessment.

TABLE I. *Patient characteristics (mean ± SD). STAI = State-trait anxiety inventory; DSST = digit–symbol substitution test*

	Sublingual lormetazepam + placebo i.v.	Sublingual placebo + diazepam i.v.
Age (yr)	23.21±2.74	23.15±3.15
Height (cm)	65.00±4.08	63.95±2.52
Weight (kg)	61.85±7.45	57.91±7.38
Trait anxiety (STAI)	38.58±11.62	34.00±6.79
Corah anxiety score	9.44±3.05	9.40±3.53
DSST (score/90 s)	59.49±8.30	56.50±13.28
Sex (M/F)	3/16	3/17

Surgeon's ratings

Two VAS scales showed poor inter-rater reliability: "ease of access" (Pearson $r = 0.16$, ns), and "degree of ptosis" ($r = -0.21$, ns) and data from these scales were not analysed. VAS ratings of anxiety ($r = 0.41$, $P < 0.01$), co-operation ($r = 0.60$, $P < 0.001$), relaxation ($r = 0.50$, $P < 0.001$) and degree of swallowing ($r = 0.40$, $P < 0.01$), hand/arm movement ($r = 0.44$, $P < 0.001$) and phonation ($r = 0.75$, $P < 0.001$) showed somewhat better agreement between raters, as did global impression of sedation ($r = 0.67$, $P < 0.001$). Sublingual lormetazepam sedation was comparable to i.v. diazepam sedation for all of the above ratings and the global impression ratings, for both surgeons.

Both surgeons rated the two treatments as good or satisfactory in the majority of patients (17 of 19 for lormetazepam and 18 of 20 for diazepam). Sedation with i.v. diazepam was rated as poor in two female patients, both of whom had high preoperative state anxiety (STAI = 68, 53). One of these failed to return for follow-up assessment while the other, who had a marked fear of dentistry (Corah = 16), subsequently rated the operation as "better" than expected, sedation as "good", and expressed a preference for "this type of sedation" in future. The two patients for whom lormetazepam sedation was rated as poor were female with high levels of preoperative state anxiety (STAI = 60, 46). They rated the operation as "worse than expected" and sedation as "good", but expressed a preference for another method of sedation in future.

Patient ratings

Following sublingual lormetazepam, two patients rated sedation as poor, four as satisfactory and 11 as good. In contrast, all patients rated sedation as good following i.v. diazepam ($P < 0.02$). Five patients in the lormetazepam group rated the operation as "worse than expected",

TABLE II. *Percent* (n) *of patients experiencing postoperative symptoms on the evening of surgery. No significant treatment differences were found. Four patients failed to return for assessment*

	Sublingual lormetazepam +i.v. saline ($n = 17$)				Sublingual placebo +i.v. diazepam ($n = 18$)			
Symptom	Not at all	Somewhat	Moderately so	Very much so	Not at all	Somewhat	Moderately so	Very much so
Tired	0.0 (0)	23.5 (4)	41.2 (7)	35.3 (6)	11.1 (2)	33.3 (6)	16.7 (3)	38.9 (7)
Confused	70.6 (12)	23.5 (4)	0.0 (0)	5.9 (1)	66.7 (12)	16.7 (3)	11.1 (2)	5.6 (1)
Sick	47.1 (8)	17.6 (3)	23.5 (4)	11.8 (2)	61.1 (11)	16.7 (3)	16.7 (3)	5.6 (1)
In pain	0.0 (0)	23.5 (4)	35.3 (6)	41.2 (7)	5.6 (1)	38.9 (7)	22.2 (4)	33.3 (6)
Normal	35.3 (6)	29.4 (5)	5.9 (1)	29.4 (5)	22.2 (4)	38.9 (7)	22.2 (4)	16.7 (3)

TABLE III. *Mean* (±*SD*) *scores on anxiety and tension scales before (pre-med.) 30 min (preoperative) and 120 min (postoperative) after sublingual administration.* *P < *0.05*; **P < *0.01*; ***P < *0.001 for ANOVA comparisons with baseline. No significant differences between treatments were found*

Assessment	Time	Lormetazepam +placebo i.v.	Placebo+ diazepam i.v.
STAI score	Pre-med.	40.8±12.3	42.9±10.9
	30 min	34.7±9.3**	35.1±9.5***
	120 min	32.8±17.6*	29.9±10.1***
VAS anxiety score (mm)	Pre-med.	53.2±29.5	58.2±27.4
	30 min	44.5±29.4	34.1±24.5***
	120 min	32.2±33.7*	22.1±19.7***
VAS tension score (mm)	Pre-med.	44.1±25.9	56.7±29.2
	30 min	28.8±19.7***	29.3±17.1***
	120 min	23.3±17.1*	20.9±13.5***

whereas all the diazepam patients rated the operation as "better than expected" ($P < 0.05$). All patients in the diazepam group expressed a preference for "this type of sedation", compared with six of 17 following sublingual lormetazepam ($P < 0.05$). The majority of patients experienced pain and fatigue on the evening of surgery, while all postoperative symptoms were equally common following both treatments (table II).

Patient anxiety

As shown in table III, anxiety levels were comparable for the two groups before administration of the wafers. Compared with baseline, significant comparable reductions in anxiety (STAI) and tension (VAS) were seen following both lormetazepam and placebo at 30 min (table III). VAS-rated anxiety at 30 min showed a significant decrease following placebo only.

Psychomotor performance

Compared with placebo, performance on the DSST showed highly significant deterioration ($P < 0.005$) at 30 min after sublingual lormetazepam, indicating rapid onset of drug effects (fig. 1). This decrease in performance was accompanied by decreased subjective alertness and quick-wittedness (fig. 1), but these latter effects were not significantly greater than those following placebo. After operation, scores on the DSST were significantly lower than control values 120 min following both treatments ($P < 0.01$) and the diazepam group, but not the lormetazepam group, were more drowsy and mentally slow than at baseline.

Amnesia

Visual memory test. Recall of premedication cards, an index of normal lack of memory, was good in both groups (table IV). The majority of patients correctly recognized five or six cards from a possible six. By contrast, significant amnesia was seen following both treatments ($P < 0.001$), with the majority of patients accurately recalling only two cards or less of those previously shown after sedation. Thus, the level of amnesia 40 min after sublingual lormetazepam was comparable to that seen 5 min after i.v. diazepam.

Memory questionnaire. Most patients in both groups recalled the administration of wafers before operation (fig. 2). Whereas all patients who had received sublingual placebo recalled the i.v. injection, only 12 of the 19 who had been given lormetazepam recalled this "perfectly" ($P < 0.05$). Amnesia for local anaesthetic, drilling and extraction was comparable following both treatments.

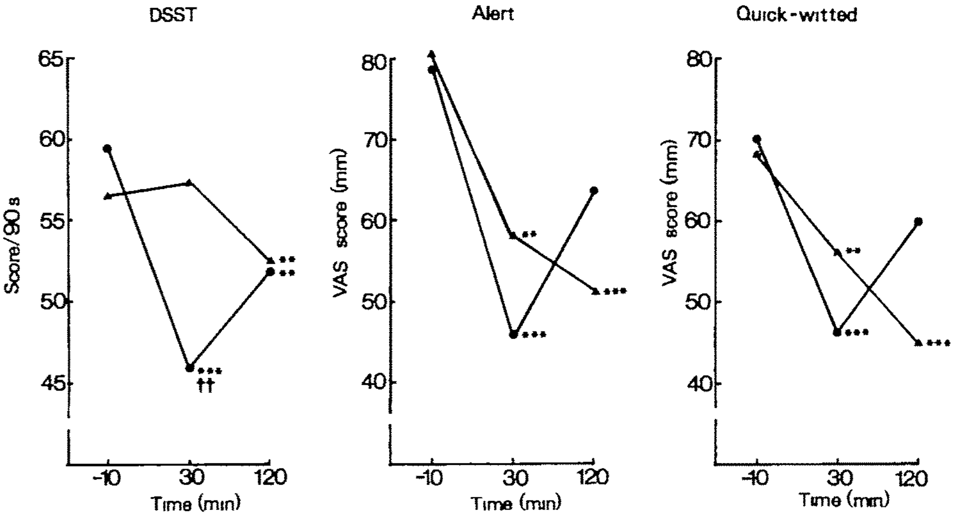

FIG. 1. Sedation: Mean scores on the DSST and on "alert" and "quick-witted" visual analogue scales at premedication (−10 min); pre-i.v. treatment (30 min) and after operation (120 min). **$P < 0.01$; ***$P < 0.001$ for paired t test comparisons with baseline. ††$P < 0.01$ for t test comparisons between treatment groups. ●——● = Sublingual lormetazepam + i.v. saline; ▲——▲ = Sublingual placebo + i.v. diazepam.

TABLE IV. *Visual memory test: percent of patients accurately recalling 0–6 cards at 1 week. Cards were previously shown at premedication and either at 40 min after sublingual lormetazepam 2.5 mg or 5 min after diazepam 10 mg i.v.* ***P < 0.001 *for non-parametric comparisons between pre- and post-medication scores*

		Number of cards accurately recalled						
		0	1	2	3	4	5	6
Lormetazepam	Pre-med.	0.0	0.0	5.9	0.0	5.9	64.7	23.5***
	Post-med.	23.5	11.8	23.5	5.9	29.4	5.9	0.0
Diazepam	Pre-med.	0.0	0.0	0.0	0.0	11.1	44.4	44.4***
	Post-med.	33.3	33.3	16.7	11.1	0.0	0.0	5.6

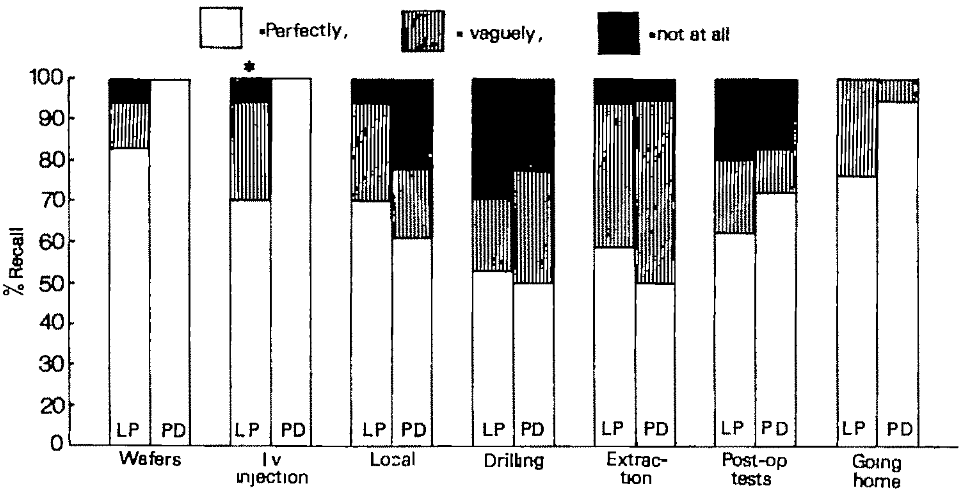

FIG. 2. Patients' recall of specific operative events for the lormetazepam (LP) and the diazepam (PD) treatment conditions. $P < 0.05$ for Chi-square comparison between treatments.

TABLE V. *Mean* (±*SD*) *heart rate* (*HR*) (*beat* min^{-1}), *systolic and diastolic arterial pressure* (*SAP*, *DAP*) (*mm Hg*) *for the lormetazepam* (*LP*) *and diazepam* (*PD*) *treatment groups.* *P < *0.05 for ANOVA pairwise contrasts between treatment groups.* ***P < *0.001 for within groups intraoperative observations effects*

		Pre-sublingual	Pre-i.v.	Local analgesia	Incision	Drilling	Extraction	Suturing	Post-op.
HR	LP	75.9±8.5	77.8±9.0	80.3±16.3	94.5±14.2	97.3±15.1	96.6±16.7	90.1±14.7	83.2±15.9***
	PD	75.8±11.3	72.1±7.8*	84.7±26.7	91.0±11.9	97.5±24.5	89.6±12.7	84.9±12.3	75.8±8.8
SAP	LP	121.4±14.6	122.3±13.0	126.1±18.4	133.7±19.0	136.9±21.5	141.5±22.6	137.8±18.0	130.5±14.8***
	PD	116.4±13.9	117.7±10.8	115.3±16.6	120.7±10.8	126.4±10.8	125.5±10.3	123.3±8.5	119.0±9.9
DAP	LP	75.7±13.2	71.8±11.5	74.6±12.4	71.4±13.1	77.5±14.3	75.7±14.5	74.1±14.5	73.6±12.3***
	PD	71.6±8.5	66.6±7.9	63.5±7.2	62.1±7.4	69.0±10.5	69.0±6.3	65.8±6.3	67.9±5.9

Cardiovascular function

The design of the study necessitated analysing preoperative and intraoperative data separately. Consequently, a 2 (treatments: placebo/lormetazepam) ×20 (patients) ×2 (observations: pre-sublingual/30 min after medication) analysis of variance (ANOVA), with repeated measures on the observations factor was conducted on preoperative data. Compared with placebo, lormetazepam had no effect on preoperative cardiovascular function (table V). Diastolic arterial pressure (DAP) showed a significant decrease from baseline to before the i.v. injection ($P < 0.008$) in both groups (mean decreases: lormetazepam group 3.9 mm Hg, diazepam group 5.0 mm Hg).

Analysis of intraoperative data was designed to determine if sublingual lormetazepam and i.v. diazepam differed in their effect on cardiovascular function during the operation. Analysis of changes from baseline during surgery showed the two treatments to be comparable in their effects. Significant observations effects were found for systolic arterial pressure (SAP) ($P < 0.001$), DAP ($P < 0.001$), and heart rate (HR) ($P < 0.001$). These results reflect progressive increases in cardiovascular arousal as surgery progressed, regardless of the treatment condition of the patients.

DISCUSSION

The results of this study indicate that sublingual lormetazepam 2.5 mg, in a novel wafer formulation, is comparable in some respects but inferior in others, to a 10-mg dose of i.v. diazepam for conscious sedation in patients undergoing oral surgery. Compared with placebo, onset of action of lormetazepam was rapid, with significant impairment in DSST in addition to significant amnesia occurring at 30 min. This probably reflects rapid absorption of the drug following sublingual administration. Tauber and colleagues [6], in a volunteer study, found significantly higher mean plasma lormetazepam concentrations between 7 and 25 min after the wafer than after conventional oral tablet formulation. Decreased first-pass liver metabolism is thought to be the reason for higher plasma concentrations following sublingual administration [6].

The anxiolytic properties of lormetazepam have been shown in previous studies. Ulsamer and colleagues [10] demonstrated significant anxiolysis following a combination of lormetazepam 2 mg as a night-before hypnotic, 1 mg as premedication and 0.5 mg i.v. as an adjunct to spinal anaesthesia. Jacobsen and co-workers [11] showed the anxiolytic effect of oral lormetazepam 2 mg to be superior to that of diazepam 15 mg given 1.5–3 h before surgery. In the present study a marked anxiolytic response was seen following placebo and the degree of anxiolysis following lormetazepam at 35 min was not significantly greater than placebo. However, surgeons' ratings of intraoperative anxiety and relaxation indicated that sedation following lormetazepam was comparable to that following i.v. diazepam 10 mg.

Patients' ratings indicated preference for sedation with i.v. diazepam. This was reflected in greater satisfaction with diazepam, greater tolerance of the procedure and greater preference for i.v. diazepam sedation for a repeat procedure. No cardiovascular complications were found with each treatment, but as in previous studies [3, 4], progressive increases in cardiovascular arousal during the operation, were found in both treatment groups.

Amnesia is an important property of benzodiazepine sedation [12]. While amnesia is more profound following i.v. sedation [13], marked amnesia has been reported with oral midazolam [4]. In the present study, sublingual lormetazepam induced levels of anterograde amnesia comparable to those induced by i.v. diazepam.

In conclusion, the present results suggest that the novel sublingual wafer formulation of lormetazepam may have a role as a premedicant and for conscious sedation in anaesthetic practice. Further studies are needed to establish the rapidity of action of the new formulation in a variety of situations. In the present situation onset of activity was rapid, sedation was comparable to that seen following diazepam 10 mg i.v., no cardiovascular complications were seen and amnesia was produced. However, ratings of patient satisfaction favoured i.v. diazepam. Given that prolonged sedation was not seen after operation following lormetazepam at the 2.5-mg dose, a higher dose may produce better sedation without necessarily resulting in prolonged postoperative sedation.

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POSTANAESTHETIC AROUSAL TIME IN ELDERLY PATIENTS

A Double-Blind Study of Glycopyrrolate and Atropine

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SUMMARY

Postanaesthetic arousal time was studied in elderly patients given either glycopyrrolate 0.01 mg kg^{-1} or atropine 0.02 mg kg^{-1} before antagonism of neuromuscular blockade. Forty patients (age ≧ 65 yr) undergoing elective hip replacement were included in a double-blind study. Arousal was scored for 2 h after recovery using a modified scoring system. No difference in arousal time was found between the two groups.

Glycopyrrolate is a quaternary ammonium compound which does not cross the blood–brain barrier [1]. In contrast, atropine is a tertiary amine which crosses the blood–brain barrier and may produce the anticholinergic syndrome characterized by drowsiness, disorientation and hallucinations [2]. There have been three reports comparing postanaesthetic arousal time following the administration of either glycopyrrolate–neostigmine or atropine–neostigmine to antagonize neuromuscular blockade Those studies found that arousal time was faster when glycopyrrolate–neostigmine was given but only involved young healthy patients [3–5].

In geriatric patients, a fast and uncomplicated postanaesthetic arousal time is more important than in the young. This double-blind study was designed, therefore, to compare arousal times in geriatric patients anaesthetized under standardized conditions using either glycopyrrolate or atropine in combination with neostigmine to antagonize neuromuscular blockade.

PATIENTS AND METHODS

Forty elderly patients (age ≧ 65 yr) undergoing elective hip replacement were studied. Patients of ASA groups I–III were included; patients who were receiving medication acting on the central nervous system were excluded.

For premedication diazepam 0.15 mg kg^{-1} was given by mouth 1 h before induction of anaesthesia. Anaesthesia was induced with thiopentone 2–4 mg kg^{-1} followed by suxamethonium 1.5 mg kg^{-1}. After tracheal intubation anaesthesia was maintained with halothane 0.25–1.0% and 66% nitrous oxide in oxygen. Incremental doses of pethidine 10–30 mg were given when needed. Pethidine was not given in the last 30 min of anaesthesia. To maintain neuromuscular blockade pancuronium 0.1 mg kg^{-1} was given and supplemented with doses of 1–2 mg when needed.

To antagonize neuromuscular blockade, a mixture of neostigmine 0.05 mg kg^{-1} with either atropine 0.02 mg kg^{-1} or glycopyrrolate 0.01 mg kg^{-1} was given in a double-blind fashion. Neostigmine was given when the train-of-four ratio was 0.25 as monitored using a Relaxograph (Datex). Before antagonizing the neuromuscular blockade, the patient's lungs were ventilated with 100% oxygen for at least 5 min.

If an extra dose of anticholinergic was needed during or after anaesthesia, either glycopyrrolate 0.2 mg or atropine 0.4 mg was administered i.v.

Arousal following termination of anaesthesia and antagonism of neuromuscular blockade was observed and scored, as shown in table I [6], at 5, 10, 15, 20, 25, 30, 40, 50, 60, 90 and 120 min after the patient had received the mixture.

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TABLE I. *Scale for assessment of alterations in the degree of consciousness during recovery from general anaesthesia. (Modification of a scale produced by Professor B. Juhl,* M.D., *Anaesthetic Department, University Hospital, Aarhus)*

Score	Description of state of arousal
1.	Normal spontaneous activity; awake; interested in the surroundings; answers and reactions adequate.
2.	Some spontaneous activity; lies with eyes closed; sleeping; is easily contacted verbally; answers adequate.
3.	Some spontaneous activity; lies with eyes closed; sleeping; is contacted verbally; answers mumbling and with latency.
4.	No spontaneous activity; is in a deep sleep; is aroused by shouting and at the same time shaking of the arm; can obey simple commands such as: open your eyes.
5.	No spontaneous activity; reacts only to painful stimulation and then with appropriate movements.
6.	No spontaneous activity; reacts only to painful stimulation and then with simple and stereotype movements such as grimacing or flexor movements.
7.	No spontaneous activity; does not react to painful stimulation; reacts to tracheobronchial suction with uncoordinated movements.

TABLE II. *Patient data: mean age, weight, male/female ratio, duration of anaesthesia, pethidine and nicomorphine consumption and body temperature on arrival in the recovery room*

	Atropine	Glycopyrrolate
Age (yr)	73.4±6.3	72.8±5.0
Weight (kg)	66.5±13.2	69.2±12.5
Duration of anaesthesia (min)	178±37	186±52
Male/female ratio	6/12	7/13
Total dose of pethidine (mg kg^{-1} h^{-1})	0.7±0.2	0.7±0.2
Postoperative analgesic (nicomorphine) (mg kg^{-1})	0.09±0.04	0.10±0.06
Body temperature after op. (°C)	35.8±0.6	35.3±0.6

TABLE III. *Distribution of patients in the glycopyrrolate (G) and atropine (A) groups according to scores obtained*

	5		10		15		20		25		30		40		50		60		90		120	
Score	G	A	G	A	G	A	G	A	G	A	G	A	G	A	G	A	G	A	G	A	G	A
1	1	1	2	2	3	3	3	4	4	4	5	5	5	6	6	6	6	6	11	7	11	6
2	1	3	2	2	2	2	7	3	9	4	11	3	12	4	12	5	12	8	7	9	8	11
3	5	1	9	3	10	4	8	4	5	5	2	6	2	6	2	5	1	3	2	2	1	1
4	8	5	4	6	4	8	1	5	2	4	2	3	1	1	0	2	1	1	0	0	0	0
5	2	4	2	0	0	0	1	2	0	1	0	1	0	1	0	0	0	0	0	0	0	0
6	2	1	0	4	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7	1	3	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

When the patient arrived in the recovery room, body temperature was measured.

The patients received nicomorphine 0.1 mg kg^{-1} as soon as they complained of pain.

The scores were analysed using a Friedmann test and the two groups were compared using the Mann–Whitney test. $P < 0.05$ was considered significant.

RESULTS

Two patients in the atropine group were excluded because they received an incorrect dose of anticholinergic drug.

There was no significant difference between the two groups for sex, age, weight, duration of anaesthesia, dose of pethidine given during anaes-

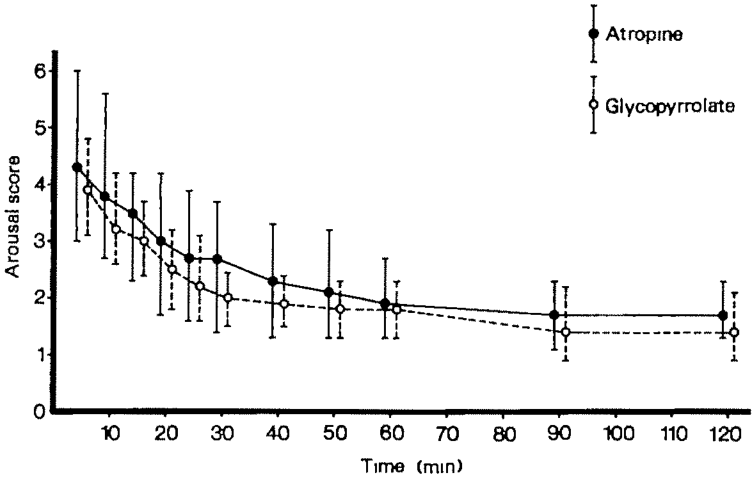

FIG. 1. Distribution of patients according to arousal scores at different times after anaesthesia. Median scores and 25 % quartiles.

thesia, body temperature on arrival at the recovering room or analgesic drug received in the recovery room (table II).

The distribution of patients of both groups according to arousal scores obtained at the different time intervals after antagonism of neuromuscular blockade is shown in table III, and figure 1 shows the median score and 25 % quartiles derived from the same data. The Friedmann test was performed for both groups and showed significant differences for both groups, indicating that, as expected, the patients progressed from higher to lower scores in the observation period ($P < 0.00025$).

Comparison of the two groups using the Mann–Whitney test showed no significant difference.

DISCUSSION

In 1966, Longo [2] described the central anticholinergic syndrome characterized by drowsiness, disorientation, loss of ability to concentrate and hallucinations. These central effects are seen when atropine is given in doses greater than 0.4 mg. Glycopyrrolate cannot cross the blood–brain barrier [1] and does not produce these central side effects.

Theoretically, it may be expected that arousal should be faster when glycopyrrolate instead of atropine is used with neostigmine to antagonize neuromuscular blockade. This was confirmed in three clinical studies [3–5], although all involved young healthy patients. In addition, Simpson, Smith and Davies [7] found that cognitive functions following general anaesthesia were less impaired when glycopyrrolate was used as the anticholinergic instead of atropine, whilst two cases of prolonged sedation in patients aged 78 yr were reported following intraoperative administration of atropine [8].

In this investigation, we have compared postanaesthetic arousal time in elderly patients following a mixture of either glycopyrrolate–neostigmine or atropine–neostigmine, but were unable to demonstrate any difference in arousal time in the two groups. The groups were comparable for age, duration of anaesthesia, doses of anaesthetic drugs given per kg of body weight and postanaesthetic analgesics given, and we attempted to standardize conditions in order to exclude some of the factors which make patients drowsy, notably poor ability to metabolize drugs, residual curarization and low body temperature. Thus: we chose a gaseous anaesthesia to exclude interference from interindividual rates of metabolizing drugs; neuromuscular blockade was monitored continuously and neuromuscular blockade was not antagonized until the TOF ratio was 0.25, to ensure that antagonism was complete; body temperature was measured on arrival in the recovery room and we found only two patients (both in the glycopyrrolate group) with a temperature less than 37 °C.

It is difficult to account for the difference between our results and those of other studies [3–5], but it may relate to variations in anaesthetic technique and degree of neuromuscular blockade. However, we studied elderly patients while the other authors examined young patients. This might partly explain our different results. All our patients received several central nervous system depressant drugs (diazepam, thiopentone, pethidine, halothane, nitrous oxide and nicomorphine). The doses of drugs and the mixture given were similar in the two groups (table II). It is possible that the slower rate of drug metabolism in the elderly may account for our inability to demonstrate any difference in the two groups, although we have no evidence for this view.

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EFFECTS OF INCREASED CARDIAC OUTPUT ON PULMONARY BLOOD FLOW DISTRIBUTION DURING LOBAR VENTILATION HYPOXIA AND COLLAPSE

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SUMMARY

Electromagnetic flow probes were placed around the pulmonary artery and left lower lobe artery in anaesthetized open-chest dogs in order to measure possible changes in the ratio of lobar-to-total pulmonary blood flow ($\dot{Q}l/\dot{Q}t$) in response to changes in cardiac output produced by the opening of arterio–venous fistulae or fluid loading. Ventilation of the lobe with 7% oxygen or lobar collapse reduced $\dot{Q}l/\dot{Q}t$ by 35% and 42%, respectively, but there were no significant changes in $\dot{Q}l/\dot{Q}t$ in response to increases in $\dot{Q}t$ of 29–133%. It is concluded that the changes in $\dot{Q}t$, pulmonary vascular pressures and mixed venous $P\text{O}_2$ within the range studied did not influence $\dot{Q}l/\dot{Q}t$.

In patients with acute respiratory failure there appears to be a direct correlation between cardiac output ($\dot{Q}t$) and right-to-left intrapulmonary shunt ($\dot{Q}s/\dot{Q}t$). Thus $\dot{Q}s/\dot{Q}t$ is increased when pulmonary blood flow is increased by fluid loading [1] or by the administration of inotropic drugs such as isoprenaline, dopamine or dobutamine [2–5]. Conversely, $\dot{Q}s/\dot{Q}t$ is reduced when pulmonary blood flow is decreased either by veno–arterial bypass [6] or by an increase in intrathoracic pressure resulting from the use of high tidal volumes or increased end-expiratory pressure during mechanical ventilation [7].

Similar changes have been observed in dogs with lungs damaged by oleic acid. Thus Smith, Cheney and Winter [8] found that $\dot{Q}s/\dot{Q}t$ varied directly with $\dot{Q}t$ when this was changed by bleeding or transfusion, whilst Lynch, Mhyre and Dantzker [9] found a similar correlation when $\dot{Q}t$ was varied by pharmacological means or by alterations in venous return. Schumacker and colleagues [10] demonstrated an increase in $\dot{Q}s/\dot{Q}t$ when $\dot{Q}t$ was increased by opening arterio–venous (A–V) fistulae in dogs with a collapsed lung. They postulated that the increase in pulmonary vascular pressures resulting from the increase in $\dot{Q}t$ decreased the magnitude of hypoxic pulmonary vasoconstriction and so increased the proportion of pulmonary blood flow distributed to the collapsed lung. In order to examine this problem in more detail, electromagnetic flow probes were used to measure the proportion of blood flow ($\dot{Q}l/\dot{Q}t$) distributed to a hypoxic left lower lobe, when $\dot{Q}t$ was increased by opening A–V fistulae and by transfusion.

MATERIALS AND METHODS

Anaesthesia was induced in 14 dogs of either sex and mixed breed (weight 19.7 ± 5.0 kg) using sodium thiopentone 20–25 mg kg^{-1} i.v. following premedication with morphine sulphate 1.5–2.0 mg kg^{-1} i.m. Anaesthesia was maintained with a continuous infusion of sodium pentobarbitone for the duration of the investigation. The trachea was intubated with a 9.0-mm i.d. cuffed tracheal tube and the lungs ventilated mechanically (Cape–Waine ventilator). Tidal volume was adjusted to give an end-tidal carbon dioxide concentration of 4.0–4.5% at a frequency of 10 b.p.m. This resulted in peak airway pressures of 10–15 cm H_2O. $F\text{I}_{O_2}$ was maintained at 1.0 and a positive end-expiratory pressure of 1.0–2.0 mm Hg was applied throughout the surgical preparation. The ECG and systemic arterial pressure were monitored continuously and body temperature was maintained at 38.0 ± 0.5 °C. Measurements of blood-gas tensions were made at regular intervals

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and base excess was adjusted to a mean value of 2.2 ± 2.2 mmol litre^{-1} by the administration of 8.4% sodium bicarbonate. A continuous infusion of Haemaccel (Hoechst U.K. Ltd) was used to replace blood loss.

Low resistance A–V fistulae were created by inserting 6–8 mm i.d. thin-walled metal tubing connected by short lengths of PVC tubing between the femoral artery and vein on each side and the right carotid artery and jugular vein. Tracheotomy was then performed and a cuffed double-lumen PVC endobronchial tube (35 FG International Catheters Corp.) was inserted to the left main bronchus. Airway pressures on each side were monitored continuously and the seal of the endobronchial cuff was verified at intervals by pressurizing one limb of the double-lumen tube whilst the other was connected to an underwater seal.

After collapsing the left lung, to improve surgical access, a left lateral thoracotomy was performed between the 5th and 6th ribs and the collapsed upper and cardiac lobes removed. This facilitated subsequent surgery and minimized vasodilator prostaglandin production as a result of handling of the left lower lobe. The pulmonary artery trunk and left lower lobe artery were freed from connective tissue and surrounded by electromagnetic flow probes (Gould–Statham SP7516 fed by synchronous excitation currents from SP2204 flowmeters). Catheters for pressure measurement and blood sampling were placed in the pulmonary arterial trunk via the stump of the left upper lobe artery, and in the left atrium via the atrial appendage. Independent control of the gas composition and ventilation of the right lung and left lower lobe were achieved by a double "bellows-in-box" system driven by the Cape–Waine ventilator at a rate of 10 b.p.m. [11]. Following the surgical preparation, the dogs were placed in the supine position and conditions allowed to stabilize for up to 2 h. During this period the left lower lobe was repeatedly ventilated with 7% oxygen in nitrogen followed by 50% oxygen in nitrogen to establish a stable response to hypoxia.

A 21-stage experimental programme was used in which each stage lasted 15–20 min, each complete study lasting 8–9 h. Control responses to left lower lobar ventilation with 7% oxygen in nitrogen were recorded at the beginning (stages 1–3) and end (stages 20–21) of each study. The effects of alterations in cardiac output were then assessed in three conditions of the left lower lobe: left lower lobar ventilation with 7% oxygen in nitrogen; lobar collapse; lobar ventilation with 50% oxygen in nitrogen. The order of the lobar conditions was randomized so that any one condition could start at either a low or high cardiac output in successive experiments. In those experiments in which lobar ventilation hypoxia (7% oxygen in nitrogen) and lobar collapse followed each other, an extra stage of lobar ventilation with 50% oxygen in nitrogen at high cardiac output (stage 9) was included. During each lobar condition cardiac output was increased by opening the arterio–venous fistulae, by fluid loading with Haemaccel to achieve the same cardiac output as was established with the fistulae, and by the combined administration of fluid and the opening of A–V fistulae. The sequence of changes was then reversed by bleeding and closing the fistulae, to return to the smallest cardiac output.

Analysis of the results was by a two-way analysis of variance using adjusted means. Differences between means were analysed by Student's t test where appropriate, a level of $P < 0.05$ being taken as significant. Sidak's inequality was applied to correct for the number of t tests used [12].

RESULTS

The only significant difference between the first and last control stages (1 and 20) was that there was a reduction in arterial pressure at stage 20 (table I). There was a significant reduction in the proportion of blood perfusing the lobe ($\dot{Q}l/\dot{Q}t$) and a reduction in lobar end-tidal $P\text{CO}_2$ (table II) in response to ventilation with 7% oxygen, but the magnitude of the response was similar throughout the investigation (stages 2, 4, 6 and 21). $\dot{Q}l/\dot{Q}t$ during collapse (stages 10–14) was significantly less than during ventilation hypoxia (stages 4–8). Mean cardiac output was increased by 29–47% by opening A–V fistulae, by 48–69% by infusing fluid, and by 115–133% using both techniques. Tranfusion, both with and without the opening of A–V fistulae, resulted in significant increases in mean pulmonary artery ($P_{\overline{\text{PA}}}$) and left atrial ($P_{\overline{\text{LA}}}$) pressures, but there were no significant changes in $\dot{Q}l/\dot{Q}t$ (fig. 1).

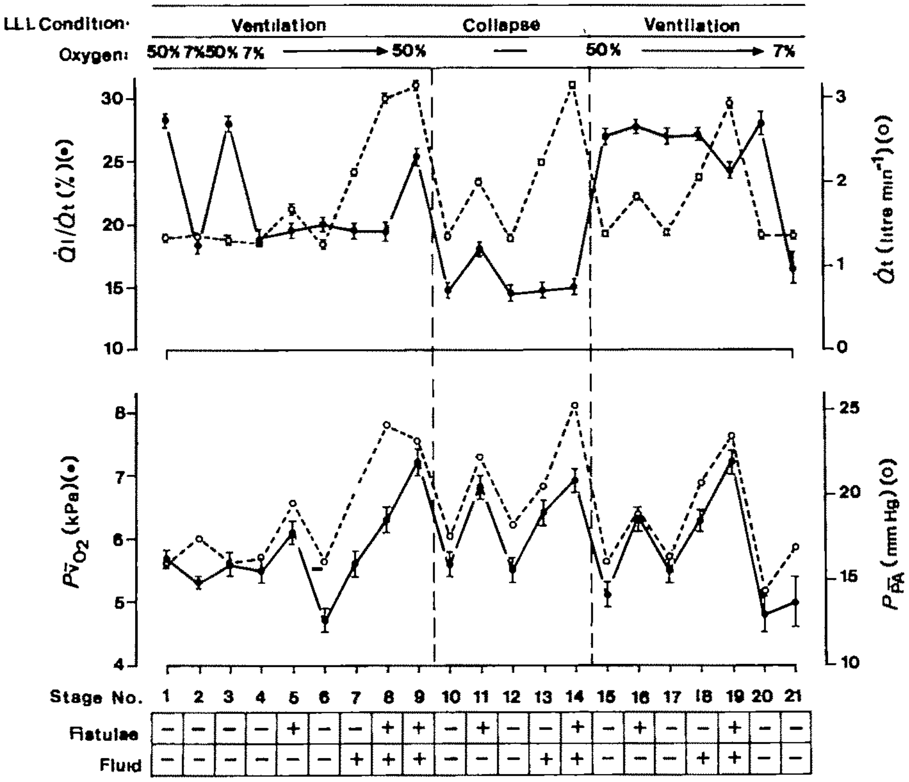
There was a small but significant increase in arterial $P\text{CO}_2$ (Pa_{CO_2}) and a reduction in pH during collapse (stages 10–14). Arterial $P\text{O}_2$ (Pa_{O_2}) was decreased by ventilation hypoxia and by collapse,

TABLE I. *Means (±SEM) of total pulmonary ($\dot{Q}t$) and lobar ($\dot{Q}l$) blood flow, mean pulmonary artery ($P_{\overline{PA}}$), left atrial ($P_{\overline{LA}}$) and carotid artery ($P_{\overline{CA}}$) pressures, and right mean airway pressure ($P_{\overline{raw}}$) during various conditions of the left lower lobe (LLL). V = Ventilation; + = A–V fistulae (Fist.) were opened or blood volume increased (Fluid). Statistically significant differences between stages ($P < 0.05$) indicated by the numbers in parentheses*

LLL condition	Fist.	Fluid	*n*	$\dot{Q}t$ (litre min^{-1})	$\dot{Q}l/\dot{Q}t$ (%)	$P_{\overline{PA}}$ (mm Hg)	$P_{\overline{LA}}$ (mm Hg)	$P_{\overline{CA}}$ (mm Hg)	$P_{\overline{raw}}$ (mm Hg)
1. 50% O_2 V	–	–	14	1.31 ±0.10	28.6 ±1.1	15.8 ±0.8	5.6 ±0.6	107.6 ±3.6	5.6 ±0.2
2. 7% O_2 V	–	–	7	1.32 ±0.14	18.5 ±1.7	17.3 ±1.2	5.3 ±0.9	108.1 ±5.3	5.3 ±0.2
3. 50% O_2 V	–	–	7	1.29 ±0.14	28.0 ±1.7	16.0 ±1.2	5.2 ±0.9	102.5 ±5.3	5.6 ±0.2
4. 7% O_2 V	–	–	11	1.29 ±0.11	19.0 ±1.3	16.2 ±1.0	4.4 ±0.7	90.2 ±4.2	5.6 ±0.2
5. 7% O_2 V	+	–	10	1.66 ±0.12	19.5 ±1.4	19.4 ±1.0	4.8 ±0.8	88.7 ±4.4	5.6 ±0.3
6. 7% O_2 V	–	–	10	1.23 ±0.12	19.9 ±1.4	16.0 ±1.0	4.0 ±0.8	84.6 ±4.5	5.9 ±0.3
7. 7% O_2 V	–	+	11	2.08 ±0.11 (4, 6)	19.4 ±1.4	20.2 ±1.0 (4, 6)	7.2 ±0.7 (4, 6)	101.4 ±4.2 (6)	5.6 ±0.2
8. 7% O_2 V	+	+	7	2.94 ±0.14 (4–7)	19.4 ±1.7	23.9 ±1.2 (4–6)	8.0 ±0.9 (4–6)	96.9 ±5.3	5.6 ±0.2
9. 50% O_2 V	+	+	6	3.09 ±0.16 (1, 3, 20)	25.2 ±1.8	23.3 ±1.3 (1, 3, 20)	9.0 ±1.0 (1, 3, 20)	96.5 ±5.8	6.0 ±0.2
10. Collapse	–	–	11	1.33 ±0.11	14.7 ±1.3 (4–8, 15–19)	17.5 ±1.0	5.5 ±0.7	104.8 ±4.2	5.4 ±0.2
11. Collapse	+	–	11	1.96 ±0.11 (10, 12)	17.9 ±1.3 (4–8, 15–19)	22.2 ±1.0 (10, 12)	6.9 ±0.7	99.0 ±4.2	5.5 ±0.2
12. Collapse	–	–	10	1.30 ±0.12	14.4 ±1.4 (4–8, 15–19)	18.1 ±1.0	5.6 ±0.7	101.5 ±4.4	5.6 ±0.2
13. Collapse	–	+	11	2.2 ±0.11 (10, 12, 14)	14.7 ±1.4 (4–8, 15–19)	20.5 ±1.0	7.9 ±0.7	114.8 ±4.2 (11)	6.0 ±0.2
14. Collapse	+	+	8	3.10 ±0.13 (10–13)	14.9 ±1.6 (4–8, 15–19)	25.2 ±1.2 (10, 12, 13)	9.7 ±0.8 (10, 12)	103.8 ±5.0	5.8 ±0.2
15. 50% O_2 V	–	–	10	1.35 ±0.12	27.1 ±1.4 (4–8)	15.9 ±1.0	4.1 ±0.8	84.3 ±4.4	5.7 ±0.3
16. 50% O_2 V	+	–	13	1.81 ±0.10 (15)	27.8 ±1.2 (4–8)	19.1 ±0.9	6.4 ±0.6	89.5 ±3.8	5.8 ±0.3
17. 50% O_2 V	–	–	10	1.38 ±0.12	27.0 ±1.4 (4–8)	16.2 ±1.0	5.8 ±0.7	92.0 ±4.4	5.7 ±0.3
18. 50% O_2 V	–	+	11	2.04 ±0.11 (15, 17)	27.2 ±1.3 (4–8)	20.5 ±1.0 (15, 17)	9.6 ±0.7 (15–17)	105.6 ±4.2 (15, 16)	5.7 ±0.3
19. 50% O_2 V	+	+	6	2.90 ±0.16 (15–18)	24.3 ±1.8 (4–8)	23.3 ±1.3 (15, 17)	9.3 ±1.0 (15–17)	91.5 ±5.8	6.4 ±0.3
20. 50% O_2 V	–	–	5	1.35 ±0.17	28.2 ±2.0	14.2 ±1.5	4.7 ±1.1	71.5 ±6.3 (1)	5.5 ±0.3
21. 7% O_2 V	–	–	3	1.36 ±0.22	16.5 ±2.6 (20)	16.8 ±1.9	3.8 ±1.4	83.9 ±8.1	5.9 ±0.4

TABLE II. *Mean values* ± *SEM of blood-gas tensions, pH, right and left end-tidal* $P\text{CO}_2$ *(*$P\text{E}'_{\text{CO}_2}$*) et each stage of the experiment. Abbreviations as in table I*

LLL Condition	Fist.	Fluid	*n*	Pa_{O_2} (kPa)	Pa_{CO_2} (kPa)	pH	$P\bar{v}_{O_2}$ (kPa)	$P\bar{v}_{CO_2}$ (kPa)	$P\text{E}'_{CO_2}$(kPa)	
									Right	Left
1. 50% O_2 V	–	–	14	34.3 ±1.4	4.7 ±0.2	7.46 ±0.01	5.7 ±0.2	5.5 ±0.2	4.6 ±0.2	4.6 ±0.2
2. 7% O_2 V	–	–	7	22.0 ±2.0 (1, 3)	4.6 ±0.3	7.44 ±0.02	5.3 ±0.2	5.2 ±0.3	4.8 ±0.2	3.6 ±0 2 (1)
3. 50% O_2 V	–	–	7	35.2 ±2.0	4.8 ±0.3	7.45 ±0.02	5.6 ±0.2	5.2 ±0.3	4.5 ±0.2	4.3 ±0.2
4. 7% O_2 V	–	–	11	22.7 ±1.6 (3, 15–19)	4.7 ±0.2	7.41 ±0.02	5.0 ±0.2	5.7 ±0.2	4.6 ±0.2	3 9 ±0.2
5. 7% O_2 V	+	–	10	20.3 ±1.7 (3, 15–19)	4.9 ±0.2	7.39 ±0.02	6.1 ±0.2 (4, 6)	5.7 ±0.3	4.6 ±0.3	4.1 ±0.3
6. 7% O_2 V	–	–	10	18.9 ±1.7 (3, 15–19)	4.9 ±0.2	7.39 ±0.02	4.7 ±0.2	5.8 ±0.3	4.7 ±0.3	4.0 ±0.3
7. 7% O_2 V	–	+	11	21.9 ±1.7 (3, 15–19)	5.0 ±0.2	7.37 ±0.02	5.6 ±0.2 (6)	5.6 ±0.3	4.8 ±0.3	4 0 ±0.3
8. 7% O_2 V	+	+	7	24.1 ±2.0 (3, 15–19)	4.7 ±0.3	7.42 ±0.02	6.3 ±0.2 (4, 6, 7)	5.1 ±0.3	4.6 ±0.3	4.1 ±0.3
9. 50% O_2 V	+	+	6	34.4 ±2.0	4.8 ±0.3	7.41 ±0.02	7.2 ±0.2 (1–8)	5.4 ±0.3	4.9 ±0.3	4.8 ±0.3
10. Collapse	–	–	11	20.7 ±1.6 (15–19)	5.3 ±0.2 (4–8)	7.37 ±0.02 (4–8)	5.6 ±0.2	6.2 ±0.2 (4–8)	4.9 ±0.2	—
11. Collapse	+	–	11	22.8 ±1.6 (15–19)	5.4 ±0.2 (4–8)	7.36 ±0.02 (4–8)	6.8 ±0.2 (10, 12)	6.0 ±0.2 (4–8)	5.1 ±0.2	—
12. Collapse	–	–	10	21.2 ±1.7 (15–19)	5.4 ±0.2 (4–8)	7.37 ±0.02 (4–8)	5.5 ±0.2	6.4 ±0.3 (4–8)	4.9 ±0.3	—
13. Collapse	–	+	11	25.6 ±1.6 (15–19)	5.5 ±0.2 (4–8)	7.36 ±0.02 (4–8)	6.4 ±0.2 (10, 12)	6.2 ±0.2 (4–8)	5.2 ±0.2	—
14. Collapse	+	+	8	24.5 ±2.0 (15–19)	5.3 ±0.2 (4–8)	7.37 ±0.02 (4–8)	6.9 ±0.2 (10, 12)	5.8 ±0.2 (4–8)	5.2 ±0.3	—
15. 50% O_2 V	–	–	10	36.9 ±1.6	5.1 ±0.2	7.41 ±0.02	5.1 ±0.2	5.9 ±0.2	4.9 ±0.3	4.9 ±0.3 (4–8)
16. 50% O_2 V	+	–	13	34.0 ±1.5	5.0 ±0.2	7.42 ±0.01	6.3 ±0.2 (15, 17)	5.9 ±0.2	4.8 ±0.3	4.7 ±0.3 (4–8)
17. 50% O_2 V	–	–	10	33.4 ±1.8	5.1 ±0.2	7.39 ±0 02	5.5 ±0.3	6.2 ±0.3	5.0 ±0.3	5.2 ±0.3 (4–8)
18. 50% O_2 V	–	+	11	33.9 ±1.6	5.4 ±0.2	7.35 ±0.02	6.3 ±0.2 (15, 17)	6.2 ±0.2	5.3 ±0.3	5.3 ±0.3 (4–8)
19. 50% O_2 V	+	+	6	33.8 ±1.9	5.1 ±0.2	7.38 ±0.02	7.2 ±0.2 (15, 17, 18)	5.7 ±0.3	.5.2 ±0 3	5.1 ±0.3 (4–8)
20. 50% O_2 V	–	–	5	33.5 ±2.4	5.0 ±0.3	7.40 ±0.02	4.8 ±0.3	6.2 ±0.4	4.6 ±0.3	4.7 ±0.3
21. 7% O_2 V	–	–	3	23.4 ±3.7 (20)	5.2 ±0.4	7.35 ±0.03	5.0 ±0.4	6.3 ±0.5	4.7 ±0 4	3.8 0.4



Stage No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Fistulae	−	−	−	−	+	−	−	+	+	−	+	−	−	+	−	+	−	−	+	−	−
Fluid	−	−	−	−	−	−	+	+	+	−	−	−	+	+	−	−	−	+	+	−	−

FIG. 1. Changes in cardiac output ($\dot{Q}t$), lobar-to-total blood flow ratio ($\dot{Q}l/\dot{Q}t$) mixed venous oxygen tension ($P\bar{v}_{O_2}$), and mean pulmonary artery pressure ($P_{\overline{PA}}$) at each stage of the experiment.

but did not change with the increase in cardiac output. Mixed venous Po_2 ($P\bar{v}_{O_2}$) increased significantly in response to the increases in Qt.

DISCUSSION

Lobar ventilation with 7% oxygen or lobar collapse produced decreases in $\dot{Q}l/\dot{Q}t$ of 35 and 42%, respectively. However, graded increases in cardiac output produced by opening A–V fistulae, fluid loading or the combination of both these interventions failed to alter $\dot{Q}l/\dot{Q}t$ even though mean pulmonary artery pressure and mixed venous Po_2 also increased. Likewise, $\dot{Q}l/\dot{Q}t$ was not changed when $\dot{Q}t$ was increased during ventilation of the lobe with 50% oxygen. Since these results are at variance with previous clinical and experimental observations, it is first necessary to consider the validity of the experimental model used.

The open-chest left lower lobe preparation enabled accurate measurements of lobar and total pulmonary blood flow to be obtained. However, there are a number of disadvantages to the use of this preparation. First, the chest is open, so that the normal vertical gradient of transpulmonary pressure, and hence of lung volume, is abolished. Second, the loss of the subatmospheric intrathoracic pressure and the necessity for a greater depth of anaesthesia decrease cardiac output, an effect which is further accentuated by blood loss. Third, the removal of the left upper and middle lobes reduces total vascular volume so that changes in $\dot{Q}t$ may produce larger changes in $P_{\overline{PA}}$ than would occur in the intact preparation. Fourth, the lungs are probably denervated during the placement of the flow probes, whilst handling of the lobe may result in the release of vasodilator prostaglandins which may decrease hypoxic pulmonary vasoconstriction. The design of the study imposed further limitations on the validity of the model. The insertion of the A–V fistulae necessitated heparinization, which made haemostasis more difficult, whilst perfusion through the external circuit may have reduced the degree of hypoxic pulmonary vasoconstriction [13]. The repeated stages of fluid loading necessitated the addition, and removal, of up to 1.5 litre of fluid and, although this was subsequently returned to the animal, there were substantial reductions in haemoglobin concentration. This reduced the oxygen-carrying capacity of the blood and increased the probability of errors in the measurement of oxygen content. In order to minimize the effects of the low haemoglobin concentration, the order in which the lobar conditions were applied was randomized and data for any set of measurements where the mean arterial pressure was less than 60 mm Hg were excluded. This reduced the number of complete studies to 7.

Comparison of the present results with those reported previously must take into consideration the magnitude and stability of the hypoxic pulmonary vasoconstrictor response and the extent of the cardiovascular changes induced by the manipulations of $\dot{Q}$t. Ventilation of the left lower lobe with 7% oxygen resulted in a decrease in $\dot{Q}$l/$\dot{Q}$t of 35% at the beginning of the investigation and of 41% at the end, whilst collapse resulted in a 42% reduction in $\dot{Q}$l/$\dot{Q}$t. The reduction in $\dot{Q}$l/$\dot{Q}$t is slightly less than the 45–55% recorded in other studies with lobar ventilation hypoxia [14–20], but was maintained throughout the experiment. Most studies report a greater reduction in $\dot{Q}$l/$\dot{Q}$t with collapse than with ventilation with 7% oxygen at a normal alveolar $P\mathrm{CO}_2$. However, studies in our laboratory have shown that ventilation with 7% oxygen in nitrogen produces alveolar and pulmonary venous $P\mathrm{O}_2$ values which are close to normal mixed venous $P\mathrm{O}_2$. Thus, the stimulus for hypoxic pulmonary vasoconstriction should be the same during ventilation with 7% oxygen as during collapse. Although earlier workers believed that the greater reduction in blood flow during collapse was the result of mechanical deformation of the vessels and of a reduction in the calibre of extra-alveolar vessels resulting from the reduced transpulmonary pressure and lung volume, it is now believed that the reduction in flow is the result of the difference in alveolar $P\mathrm{CO}_2$, $P\mathrm{CO}_2$ during ventilation hypoxia being close to arterial $P\mathrm{CO}_2$, whilst the lobe equilibrates with mixed venous $P\mathrm{CO}_2$ during collapse. The greater $P\mathrm{CO}_2$ during collapse augments the hypoxic pulmonary vasoconstrictor response and so results in a greater reduction in $\dot{Q}$l/$\dot{Q}$t [18].

Although the pulmonary arterial and left atrial pressures suggest that blood replacement was adequate, the initial cardiac output values were lower than those commonly observed in anaesthetized closed-chest animals. The increases in $\dot{Q}$t produced by opening A–V fistulae or infusing fluid are relatively small but, with open fistulae plus fluid loading, $\dot{Q}$t was increased by 115–133%. These increases were accompanied by an increase in $P_{\overline{\mathrm{PA}}}$ of 6–7 mm Hg and $P_{\overline{\mathrm{LA}}}$ of 4–5 mm Hg, but no change in $\dot{Q}$l/$\dot{Q}$t. These observations contrast with those of Shumacker and colleagues [10] who measured the change in shunt ($\dot{Q}$s/$\dot{Q}$t) in response to the opening of A–V fistulae in dogs with collapse of the whole left lung in the closed chest. They had a smaller increase in $\dot{Q}$t (65%), but a similar increase in $P_{\overline{\mathrm{PA}}}$ (from 16 to 22 mg Hg), and found that Qs/Qt was increased from 33 to 43%. However, these authors noted, in four animals with high shunt values after collapse (mean 46%), that there was no change in $\dot{Q}$s/$\dot{Q}$t in response to the increase in $\dot{Q}$t, whilst in the remaining six animals $\dot{Q}$s/$\dot{Q}$t increased from 24 to 42%, the increase in $P_{\overline{\mathrm{PA}}}$ being the same in both groups of animals. On the basis of these observations, the authors postulated that the group of animals with the low initial shunt values had active hypoxic pulmonary vasoconstriction and that this became less effective when opposed by the increase in $P_{\overline{\mathrm{PA}}}$ resulting from the increase in Qt.

The difference in results between the two studies could be attributable to several factors. First, Schumacher and colleagues [10] used measurements of shunt made by an inert gas technique to quantify the redistribution of blood flow. This technique would have detected sources of right-to-left shunt outside the collapsed left lung and these might have been increased with the increases in $\dot{Q}$t. Second, there may have been a difference in the magnitude of the hypoxic pulmonary vasoconstrictor response between the two studies, for it is known that the diversion of blood flow in response to hypoxia is reduced when the volume of lung made hypoxic is large [16, 17]. Third, it has been shown that collapse in the closed chest results in a lower absolute pressure over the area of collapse, thus increasing transpulmonary pressure and expanding extra-alveolar vessels with a consequent increase in flow to the collapsed area of lung [21]. Collapse in the closed chest may also result in over-expansion of the inflated lung which may, in turn, tend to shift blood flow into the collapsed lung [22]. The increase in intravascular pressures as a result of the very dependent position of the collapsed lobe in the chest cavity may also have opposed hypoxic pulmonary vasoconstriction [14]. Finally, the influence of mixed venous $P{O_2}$ must be considered. This is relatively unimportant in the ventilated lobe, but governs the magnitude of constriction in the collapsed lobe [23, 24]. However, as the increase in $P\bar{v}_{O_2}$ was similar in both studies (from approximately 5 to 7 kPa), this is unlikely to have caused the difference in the results.

Other authors have demonstrated a direct relationship between $\dot{Q}s/\dot{Q}t$ and $\dot{Q}t$ in oleic acid-induced lung damage in dogs. Thus Lynch, Mhyre and Dantzker [9] decreased $\dot{Q}t$ by inflating balloons in the inferior vena cava and by the administration of pentobarbitone, and increased $\dot{Q}t$ by the infusion of dopamine. These interventions resulted in changes in $\dot{Q}s/\dot{Q}t$ from 63 to 105% of control values. Smith, Cheney and Winter [8] dissociated the effects of $\dot{Q}t$ and $P\bar{v}_{O_2}$ by veno–venous shunting of blood through a disc oxygenator and showed that decreasing mixed venous saturation from 59 to 32% decreased $\dot{Q}s/\dot{Q}t$ from 29 to 26%. Subsequently, Bishop and Cheney [25], using a similar technique, showed, in dogs with oleic-acid induced lung damage, that a change in $P\bar{v}_{O_2}$ from 30 to 52 mm Hg resulted in an increase in $\dot{Q}s/\dot{Q}t$ from 39 to 43%, whilst an increase in $\dot{Q}t$ from 1.97 to 3.61 litre min^{-1} increased $\dot{Q}s/\dot{Q}t$ from 47 to 53%. Thus it appeared that the increase in $\dot{Q}s/\dot{Q}t$ associated with the increase in $\dot{Q}t$ was attributable to both the mechanical effects of the change in flow and the resulting change in $P\bar{v}_{O_2}$.

The distribution of flow between hypoxic and normoxic regions of lung depends on the regional pulmonary vascular resistances and the pressure difference between pulmonary artery and left atrium. An increase in $P_{\overline{PA}}$ resulting from an increase in Qt will result in recruitment of extra vessels and a reduction in measured PVR, even though the calibre of the perfused vessels may be unchanged. Any increase in $\dot{Q}s/\dot{Q}t$ or $\dot{Q}l/\dot{Q}t$ must, therefore, be the result either of preferential recruitment of vessels in the hypoxic areas of the lung or of distension of vessels already open. Benumof and Wahrenbrock [14] have provided evidence which suggests that hypoxic pulmonary vasoconstriction may be opposed by an increase in intravascular pressures and Lemaire [26] has pointed out that the increase in $\dot{Q}s/\dot{Q}t$ in patients is seen predominantly in those in whom there is a marked increase in $P_{\overline{PA}}$ in response to the increase in Qt. Therefore, it seems likely that the major cause of the increase in $\dot{Q}s/\dot{Q}t$ in patients is a reduction in hypoxic pulmonary vasoconstriction as a result of the increased intravascular pressures. It is also possible that the increased flow may result in an increase in alveolar oedema in the most dependent portions of the lungs [27]; however, in the majority of the studies the increase in $\dot{Q}s/\dot{Q}t$ was rapidly reversed after returning $\dot{Q}t$ to normal values.

In situations in which the change in $\dot{Q}t$ is mediated by a pharmacological intervention, there may be additional factors. Some drugs are general pulmonary vasodilators and decrease $P_{\overline{PA}}$. The vasodilatation may act preferentially on hypoxic pulmonary vessels and so increase flow to non-ventilated areas of lung [28, 29]. The reduction in $P_{\overline{PA}}$ may also decrease the perfusion of the well-ventilated non-dependent portions of lung, so that there is an apparent increase in the proportion of flow to poorly-ventilated dependent portions [30]. Other drugs such as dobutamine may have little effect on normoxic vascular tone, but may reduce hypoxic pulmonary vasoconstriction [19]. Dopamine, on the other hand, appears to have no effect on hypoxic pulmonary vasoconstriction [28], but vasoconstricts normoxic lung. This increases $P_{\overline{PA}}$ and so drives more blood to the hypoxic areas [11].

It is concluded that the increase in $\dot{Q}s/\dot{Q}t$ with increasing $\dot{Q}t$ observed in patients with acute respiratory failure could be the result of recruitment of vessels in hypoxic areas of lung because of the increase in $P_{\overline{PA}}$. The failure to observe these changes in the present investigations was probably caused by the efficiency of the hypoxic vasconstrictor mechanism and the relatively small changes in $\dot{Q}t$ and $P_{\overline{PA}}$ produced. There is evidence that the hypoxic pulmonary vasoconstrictor response is decreased in the presence of endotoxaemia [31] and in pneumococcal pneumonia [32] and it is therefore possible that an increase in $\dot{Q}t$ has a greater effect in patients with acute respiratory failure than in the experimental model described.

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EFFECT OF METHYLENE BLUE ON THE ABSORBANCE OF SOLUTIONS OF HAEMOGLOBIN

E. S. GORMAN AND M. R. SHNIDER

SUMMARY

The effect of the i.v. administration of methylene blue dye on haemoglobin oxygen saturation, measured by a pulse oximeter was investigated. The absorption spectra of various concentrations of haemoglobin, oxyhaemoglobin and methylene blue were compared. The amount of 660-nm light absorbed by methylene blue was sufficient to cause a factitious haemoglobin desaturation as measured by the pulse oximeter.

Methods for the *in vitro* and *in vivo* measurement of Po_2 and haemoglobin oxygen saturation have been available for some time. Although oximetry has evolved since Joseph Priestly discovered oxygen, the development of methods and equipment has accelerated only in the past years, culminating in the latest device, the pulse oximeter.

The *in vitro* determination of haemoglobin oxygen content began in 1900 when Haldane developed a chemical method using ferricyanide. Van Slyke developed a manometric method in 1924. Photometric methods were introduced in the 1930s, utilizing the absorbance of specific bands of light wavelengths by haemoglobin solutions or blood. The specimens were transilluminated, a photocell served as a receptor and a galvanometer quantitated the resultant current.

Reflection oximeters utilized similar principles, but the specimen was not transilluminated but merely illuminated, reflecting the non-absorbed light back to a photocell. In 1949, Brinkman and Zijlstra introduced the Neon Tube Haemoreflector based on this principle. It used a filtered neon light source which emitted light between 600 nm and 700 nm and a Kipp galvanometer to measure the voltage across a selenium barrier layer photocell.

The "Cyclops" was also developed in 1949 by Brinkman and served as a non-invasive means of quantitating the *in vivo* haemoglobin oxygen saturation during operation, thus eliminating the need for blood sampling. The apparatus was mounted in the centre of the forehead, thus acquiring its name. Its construction was slightly different from the haemoreflector because non-blood tissue would be absorbing light as well, necessitating a reference or control. The Cyclops utilized three lamps. Green light is almost completely absorbed by blood, so all reflected light was attributable to the presence of other tissue. Thus, a green light was alternated with a red light and their respective voltages compared, the difference deriving from the absorbance of the red light by blood. A third lamp was used as a compensation cell. The Cyclops was small, quantitative and a means by which many intraoperative events were documented for later study.

In 1956, Mook and Zijlstra adapted a cyclops-like oximeter to cuvettes connected to a cardiac catheter. This was called the CC Oximeter ("catheter cuvette") (Kipp and Sons, the Netherlands) and produced virtually instantaneous readings during cardiac catheterization [1–3].

Transcutaneous oxygen determination followed and utilized a modified Clark electrode which measured the oxygen which dissolved from the capillary bed through the skin. This did not measure the haemoglobin oxygen saturation, but rather an index of the oxygen tension of the patient. While this has been of some use in the paediatric patient population, there have been many drawbacks to its use [4, 5].

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Pulse oximetry, the functioning of which is described in more detail in the discussion, has proven to be an invaluable asset for the management of a variety of patients during and after operation. It is reliable, accurate, non-invasive and applicable to both adults and children. In our experience, and that of others, oximetry has allowed detection of haemoglobin desaturation before that registered by other monitors or by changes in the vital signs [6].

It has been our practice to monitor haemoglobin saturation, using a pulse oximeter, during anaesthesia in patients at high risk for developing intraoperative hypoxaemia. Included in this group are patients with significant cardiopulmonary disease, those undergoing bronchoscopy or one-lung ventilation [7], and victims of severe trauma. While the monitor appears to be highly sensitive and specific to desaturation, false positive readings may occur. We report an example of such an occurrence.

CASE REPORT

A 65-yr-old woman with no pertinent medical history was admitted to the hospital via the emergency ward following a motor vehicle accident. Her ventilatory and haemodynamic status was satisfactory. A thorough evaluation was performed. Preoperative radiographic studies revealed fractures of the right leg, forearm and hand, and a defect in the right urinary collecting system which was believed to be located in the right ureter. No other abnormalities were evident.

The patient was brought to the operating room for an exploratory laparotomy and concurrent reduction and fixation of several fractures. Monitoring for the procedure included an ECG, arterial pressure (direct), CVP, temperature, oesophageal stethoscope, and measurements of $F_{I_{O_2}}$ and end-tidal carbon dioxide concentration. A Foley catheter was inserted and a pulse oximeter placed on the right index finger. Anesthesia was induced with ketamine 70 mg and maintained with fentanyl, 50 % nitrous oxide and isoflurane in oxygen. Vecuronium (total 10 mg) was given; neuromuscular blockade was also accomplished with pancuronium. An Ohio Modulus II ventilator was utilized.

After the abdomen was opened, gross inspection failed to reveal the defect in the urinary collecting system. The surgical team then requested the i.v. administration of methylene blue to dye the patient's urine and thus locate the area of extravasation. Fifty milligram of 1 % methylene blue (5 ml) was chosen as the total dose. An initial 20 mg (2 ml) was administered as a single dose via a 14-gauge catheter placed in an antecubital vein while the patient was observed for adverse reactions; if none occurred, the remainder of the dye was to be given. Less than 1 min following this initial dose, the pulse oximeter began to display decreasing haemoglobin oxygen saturations from an initial 100 % to a nadir of 1 %. This occurred over an interval of 10–15 s then, just as rapidly, the value returned to 100 %.

A rapid and careful examination of the patient and equipment failed to reveal any defect in our ability to oxygenate the patient, nor any haemodynamic changes. A second decrease in displayed haemoglobin oxygen saturation followed several minutes later, this time to 65 %. Subsequent doses of methylene blue yielded similar readings. The remainder of the procedure was uneventful. The patient's course revealed no evidence of intraoperative hypoxaemia.

MATERIALS AND METHODS

Because the hypothesis for the factitious haemoglobin desaturation was absorption of 660-nm light by methylene blue, the absorption spectra of haemoglobin, oxyhaemoglobin and methylene

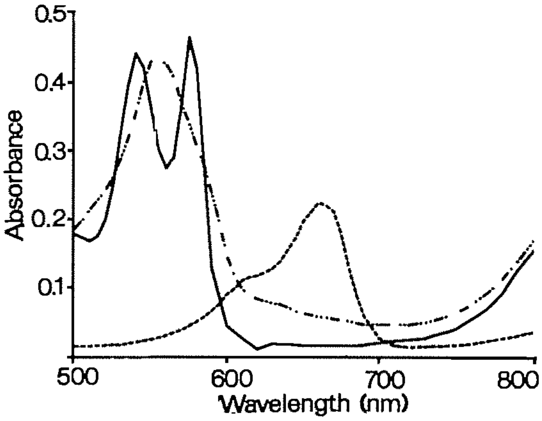

FIG. 1. The absorbance spectra of haemoglobin 0.5 mg ml^{-1} (-·-·-), oxyhaemoglobin 0.5 mg ml^{-1} (——), and methylene blue 0.001 mg ml^{-1} (---) in bicarbonate buffer 0.05 mol $litre^{-1}$. Methylene blue has a significant absorbance at 660 nm, even in extremely small concentrations. Methylene blue may thus be identified as desaturated haemoglobin by the pulse oximeter.

blue were determined (fig. 1). Haemoglobin solutions were chosen instead of whole blood because the effects of reflection, refraction and scattering caused by the non-haemoglobin components are eliminated *in vivo* by the pulse oximeter [8].

Dilutions of methylene blue were prepared containing between 1 and 10 μg ml^{-1}. The spectra were determined between 320 and 800 nm (fig. 2). The spectrum of methylene blue was very reproducible and has been documented many times in the past.

A haemoglobin solution was prepared from fresh, whole human blood. The red cells were separated from 15 ml of blood by centrifugation at 2000 *g* at 2 °C for 10 min. The plasma was discarded and the red cells resuspended in 30 ml of saline and recentrifuged. This washing procedure was repeated four times. The packed red cells were then lysed in 75 ml of distilled water. In order to separate cell debris for removal, the lysate was centrifuged at 25000 *g* at 2 °C for 15 min. The haemoglobin concentration of this solution was determined by spectrophotometry as cyanmethaemoglobin at 540 nm and the solution used as the stock solution for the experiments. Desired concentrations of haemoglobin were obtained by serial dilutions of the stock solution.

Oxyhaemoglobin solutions were prepared by equilibrating the haemoglobin solutions with oxygen at 20 °C for 30 min in an IL tonometer, model 237 (Instrumentation Laboratories Inc., Lexington, MA). Oxygen-free haemoglobin solutions were prepared by equilibrating the specimens with nitrogen for 60 min in the tonometer. We have found that such solutions prepared by equilibration with nitrogen have better spectral reproducibility than those obtained by chemical treatment using, for example, sodium hydrosulphate.

The haemoglobin solutions were transferred anaerobically from the tonometer with a 10-ml glass syringe to a closed-system spectrophotometry cell. The spectrum of each specimen was determined three times with a dual beam Beckman DB-G spectrophotometer. Distilled water was used in the reference cell for all measurements. The coefficient of variation of the readings of the same specimen varied between 0 and 0.025 at the various wavelengths and for the different specimens between 0.0921 and 0.063, indicating that the spectra of the solutions were reproducible.

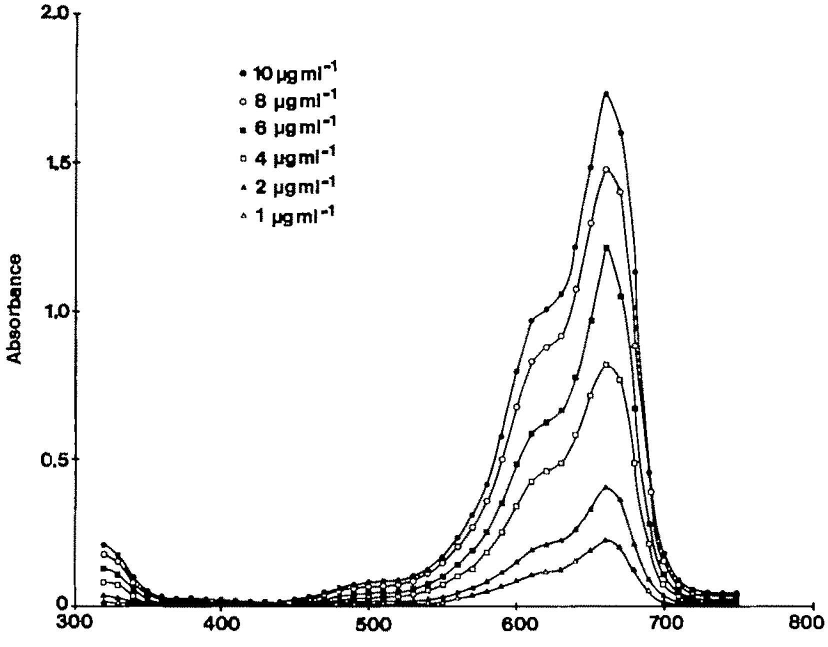

FIG. 2. The absorbance spectra of various concentrations of methylene blue. The peak absorbance occurs at 660 nm.

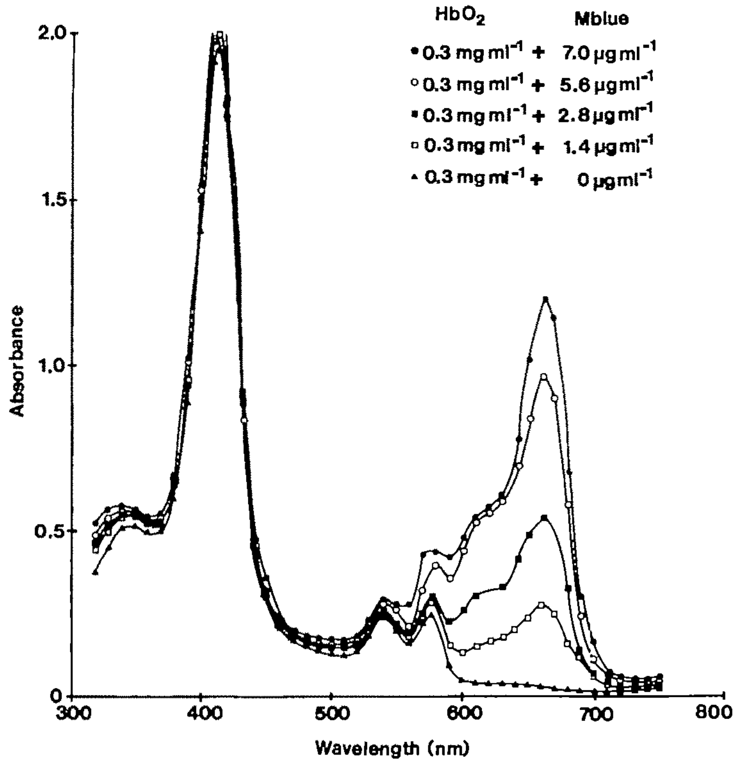

FIG. 3. The absorbance spectrum of oxyhaemoglobin 0.3 mg ml^{-1} (HbO$_2$) with various concentrations of methylene blue (MBlue). Note that the spectrum is essentially unchanged except in the 550–700 nanometer region.

Aliquots of oxyhaemoglobin 0.3 mg ml^{-1} solution were mixed with various concentrations of methylene blue (0, 1.4, 2.8, 5.6, 7.0 µg ml^{-1}) and the absorption spectra determined (fig. 3).

A 6-ml aliquot containing oxyhaemoglobin 0.2 mg ml^{-1} and methylene blue 2.8 µg ml^{-1} was incubated at 37 °C for 2 h in the presence of oxygen. It was then placed in a Spectrapor membrane tubing (mol.wt cut-off = 2000) and dialysed against three exchanges of distilled water 1 litre. The spectrum was then determined as above and compared with those of un-incubated oxyhaemoglobin 0.1, 0.2, 0.4 and 0.8 mg ml^{-1} (fig. 4).

RESULTS

The estimated peak methylene blue concentration delivered to the peripheral circulation of our patient was 2.8 µg ml^{-1}. This concentration of methylene blue absorbed significantly more 660 nm light than either haemoglobin or oxyhaemoglobin *in vitro*. From these experiments we estimate that sufficient concentrations of methylene blue were delivered to the upper extremity, where the pulse oximeter was situated, to cause a factitious desaturation measurement. It was also demonstrated that methylene blue in the concentration predicted *in vivo* does not alter the absorbance spectrum of haemoglobin—the absorbance effects are merely additive.

DISCUSSION

Saturated and desaturated haemoglobin exhibit different characteristics of absorption of the visible and infra-red light spectra. This principle is utilized by the pulse oximeter to calculate haemoglobin oxygen saturation. The pulse oximeter has two monochromatic light emitting diodes (660 nm and 940 nm) and a transducer which measures the light transmitted through tissue. These are placed in opposition, commonly over a finger-tip as in our example, but may also

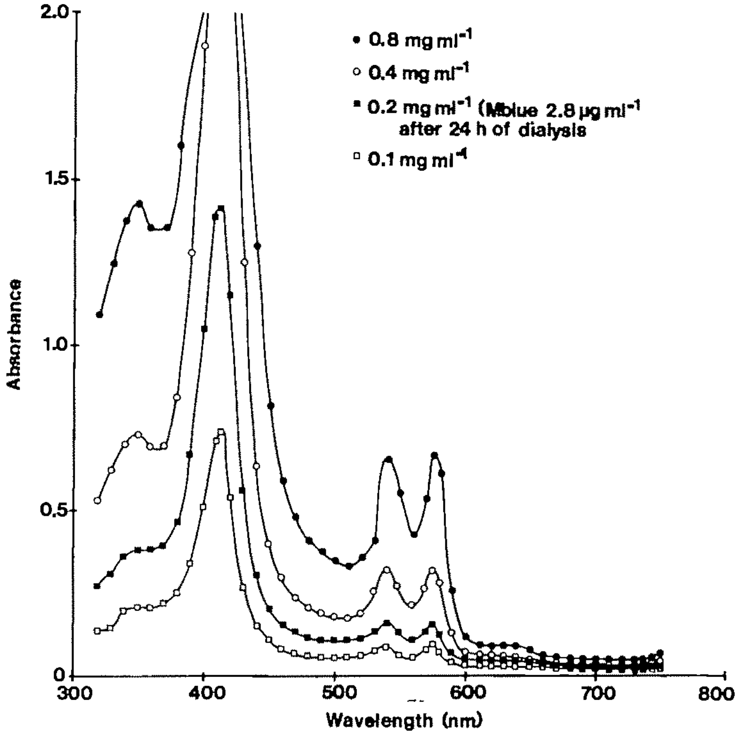

FIG. 4. The absorbance spectra of oxyhaemoglobin 0.1, 0.2, 0.4 and 0.8 mg ml^{-1}. The 0.2-mg ml^{-1} specimen was incubated with methylene blue 2.8 µg ml^{-1} for 2 h at 37 °C then dialysed for 24 h to remove the methylene blue. The spectrum is coincident with that of oxyhaemoglobin 0.2 mg ml^{-1} without incubation with methylene blue.

be placed over the bridge of the nose or pinna to transilluminate the tissue. Only light received with periodicity, pulsatile blood flow for example, is used for computation, in order to eliminate the background effects of venous blood, tissue, etc. [9]. As can be appreciated from figure 1, oxyhaemoglobin has a lesser absorption of red (660 nm) light than has haemoglobin, and thus appears red to the eye. This differential transmission through the transilluminated tissue is used to compute the degree of oxygen saturation of the blood. This information, as well as the pulse rate, is displayed on the oximeter. Various alarm settings may also be set and utilized.

Any substance that absorbs significant light of wavelength 660 or 940 nm may interfere with the accurate measurement of haemoglobin saturation by the pulse oximeter. Methylene blue absorbs significant light in the red (660) nm range.

The concentration of methylene blue in the radial artery and hence the hand was calculated from studies performed by Hamilton and colleagues [10–12], who utilized the dye "Brilliant Vital Red" in quantitating cardiac output in man and animals. The profound effect of this concentration of methylene blue on oxy- and deoxyhaemoglobin solutions was demonstrated in our present study. A bolus of this dye may, therefore, be mistakenly identified as desaturated haemoglobin in arterial blood. This is the mechanism we believe to be responsible for the observed measurements in our patient.

Other aetiologies of the apparent desaturation have been considered, but are improbable in our opinion. A true desaturation is unlikely to have occurred, because a thorough inspection of the patient and anaesthetic apparatus failed to reveal any change or defect in our ability to oxygenate the patient adequately, and the measured desaturations were closely and temporally related to the individual doses of methylene blue. In addition, the apparent desaturations occurred too rapidly, even if there had been a complete cessation of oxygen delivery to the lungs.

Another possibility considered was the conversion of oxyhaemoglobin to another species with a different absorbance spectrum, by the high local concentration of methylene blue in each bolus. We showed, however, that the addition of various concentrations of methylene blue to oxyhaemoglobin (fig. 3) does not alter its absorbance spectrum, but merely contributes its absorbance in an additive manner. As can be appreciated, extremely small concentrations of methylene blue absorb significantly in the 660-nm range.

A final possibility is that the observed phenomenon was a result of signal pick-up error. This is very common in pulse oximetry, but doubtful in our case because of the temporal relationship of the boluses to the readings described above. The presence of a second-pass effect further supports our conclusions.

Neither human nor animal experimentation has yet been undertaken to repeat these findings. It would be useful and interesting to know the effect of methylene blue and other medically useful dyes on pulse oximetry. Methylene blue is commonly utilized during surgery to locate portions of the urinary tract or to treat methaemoglobinemia,—for example that resulting from prilocaine toxicity. It is also administered before surgery to patients undergoing thyroid surgery, to highlight the parathyroid glands. Its use demands an understanding of its effects on our monitoring systems. We strongly advocate continuous intraoperative pulse oximetry in certain populations during anaesthesia; various artefactual readings, however, should be investigated and recognized in order to improve our utilization of this mode of monitoring.

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USE OF VECURONIUM AND DOXAPRAM IN PATIENTS SUSCEPTIBLE TO MALIGNANT HYPERTHERMIA

H. ØRDING AND L. FONSMARK

SUMMARY

Neuromuscular blockade was obtained with vecuronium 108 $\mu g\ kg^{-1}$ in 44 patients undergoing diagnostic muscle biopsy as part of an investigation of malignant hyperthermia (MH) susceptibility. At the termination of anaesthesia doxapram 1.43 mg kg^{-1} was given in an attempt to antagonize postoperative respiratory depression. Rectal, muscle and skin temperatures, blood lactate concentration and venous P_{CO_2} *were measured before, during and after anaesthesia. Susceptibility to MH was established by* in vitro *contracture tests according to the protocol of the European MH Group. Twenty patients were susceptible to MH (MHS), 19 were MH non-susceptible (MHN) and five MH equivocal (MHE). No adverse effects of the drugs were observed. There were no differences between the three groups in rectal or muscle temperature, blood lactate concentration or venous* P_{CO_2} *at any time. Doxapram did not prevent an increase in postoperative* P_{CO_2}. *It is concluded that vecuronium and doxapram may be safely administered to patients susceptible to MH.*

Although pancuronium is recommended [1] when neuromuscular blockade is required in patients susceptible to malignant hyperthermia (MH), a non-depolarizing drug with a shorter duration of action would be useful for surgical procedures of short duration. Atracurium has been tested without untoward effects in both pigs [2, 3] and man [4]. Vecuronium has a duration of action similar to that of atracurium, and is without any sympathomimetic side effects [5]. Therefore, it was anticipated that this drug would not trigger malignant hyperthermia in MH susceptible patients. However, this point has been questioned recently [6], on the basis of results obtained in pigs [7].

Doxapram antagonizes opioid-induced respiratory depression [8], presumably by stimulation of both peripheral and central chemoreceptors [9]. Although the overall effect of doxapram on metabolism has not been investigated, oxygen consumption is increased [10]. Convulsions are well known adverse effects of doxapram and are believed to be elicited by a general stimulatory effect on the central nervous system [11]. Since an increase in energy metabolism of skeletal muscles is an important finding during clinical MH [1], the possible indirect stimulation of muscle metabolism by doxapram could be of clinical importance, precluding its use in MH susceptible patients.

The aims of the present study were, accordingly, to assess the safety of vecuronium and doxapram administered during, and after, anaesthesia in MH susceptible patients.

PATIENTS AND METHODS

Forty-four consecutive patients, scheduled for elective muscle biopsy as part of the investigation of susceptibility to malignant hyperthermia, participated in the study after their informed consent had been obtained. The design of the study was approved by the local ethics committee. Premedication consisted of diazepam 0.3 mg kg^{-1} by mouth 1 h before the induction of anaesthesia. Anaesthesia was induced with thiopentone 4–5 mg kg^{-1} and fentanyl 0.2–0.3 mg, and was maintained with 70% nitrous oxide in oxygen.

Vecuronium 0.1 mg kg^{-1} was administered and the trachea intubated. Neuromuscular blockade

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was monitored by train-of-four nerve stimulation and tactile evaluation [12]. Ninety percent neuromuscular blockade was maintained throughout anaesthesia by the administration of supplementary doses of vecuronium 0.5–1 mg. At the end of surgery neuromuscular blockade was antagonized by neostigmine 2.5 mg (given with glycopyrrolate 0.5–0.6 mg). For antagonism of ventilatory depression a bolus dose of doxapram 1.5 mg kg^{-1} was given. When spontaneous ventilation was judged clinically to be adequate and the patients could sustain a 10-s head-lift, they were transferred to the recovery room.

Venous carbon dioxide tension ($P\text{CO}_2$), blood lactate concentration, and deep rectal, muscle and skin temperatures were measured before anaesthesia, during anaesthesia immediately before the administration of doxapram, and 15 min and 1, 2 and 4 h after the termination of anaesthesia. The blood samples were drawn from an antecubital vein.

Specimens of muscle tissue were subjected to halothane and caffeine tests as previously described [13, 14], and a diagnosis of susceptibility to MH made according to the criteria of the European MH Group [15].

For statistical analysis the Wilcoxon matched-pairs signed-ranks test, the Mann–Whitney *U* test and the Kruskal–Wallis one-way analysis of variance were applied. $P < 0.05$ was considered significant.

RESULTS

One MH susceptible patient, aged 75 yr, had moderate arterial hypertension and was, therefore, not given doxapram. Other clinical data of the patients and results of the *in vitro* test for susceptibility to MH are shown in table I. There was no statistically significant difference between the three groups in age, weight, duration of anaesthesia, and total doses of thiopentone, fentanyl, vecuronium, glycopyrrolate, neostigmine or doxapram (table I). There were no anaesthetic complications; specifically, there was no evidence of incipient MH.

There was no significant difference between the three groups in rectal or muscle temperatures at any time (fig. 1). In skin temperature, statistically significant differences between the groups were found just before the administration of doxapram, and 2 and 4 h after anaesthesia, whereas the values before, and 15 min and 1 h after anaesthesia, were not significantly different (fig. 1). The observed difference before doxapram was caused by the MHN (non-susceptible) group having a lower skin temperature than the MHS (susceptible) and MHE (equivocal) groups, whereas the differences after anaesthesia were the result of an increased skin temperature in the MHE group compared with the MHS and MHN groups.

Rectal temperature decreased significantly during anaesthesia and in the period immediately after operation in the MHS and MHN groups (fig. 1). From 1 h after the termination of anaesthesia, rectal temperature increased significantly again, but it had not reached the preanaesthetic value 4 h after anaesthesia. The number of patients in the MHE group was too limited to permit similar statistical analyses.

Muscle temperature also decreased significantly during anaesthesia in the MHS and MHN groups

TABLE I. *Results of* in vitro *test, clinical data and total doses of drugs in 44 patients investigated for susceptibility to MH (mean ± 1SD). No significant differences between groups* ($P > 0.05$). *MHS = susceptible; MHN = non-susceptible; MHE = equivocal.* †n = *19*

	Diagnosis		
	MHS	MHN	MHE
n	20	19	5
Age (yr)	33.8 ± 20.4	34.3 ± 15.2	27.0 ± 7.0
Weight (kg)	63.6 ± 16.5	66.4 ± 17.0	62.0 ± 5.2
Duration of anaesthesia (min)	47.0 ± 8.9	46.1 ± 6.7	42.8 ± 11.3
Thiopentone (mg kg^{-1})	4.9 ± 1.7	5.8 ± 2.2	6.4 ± 1.7
Fentanyl (μg kg^{-1})	4.4 ± 1.1	4.3 ± 1.5	4.3 ± 0.8
Vecuronium (μg kg^{-1})	108 ± 14	108 ± 14	107 ± 13
Glycopyrrolate (mg)	0.45 ± 0.10	0.48 ± 0.10	0.50 ± 0
Neostigmine (mg)	2.26 ± 0.50	2.39 ± 0.50	2.45 ± 0.10
Doxapram (mg kg^{-1})	1.43 ± 0.08†	1.43 ± 0.12	1.39 ± 0.11

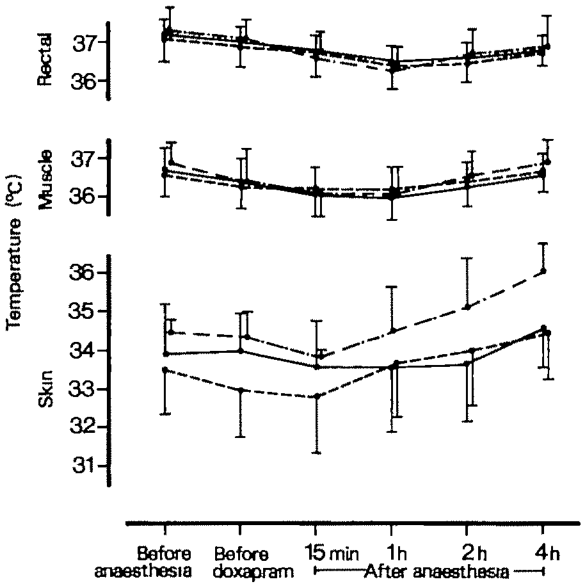

FIG. 1. Rectal, muscle and skin temperatures (mean ± 1SD) in 20 MH susceptible (——), 19 MH non-susceptible (---) and five MH equivocal (·—·—·) patients before, during and after anaesthesia. No statistically significant differences were found between groups in rectal and muscle temperatures. Skin temperature was significantly lower in MHN group before administration of doxapram and significantly higher in the MH-equivocal group 2 h and 4 h after anaesthesia.

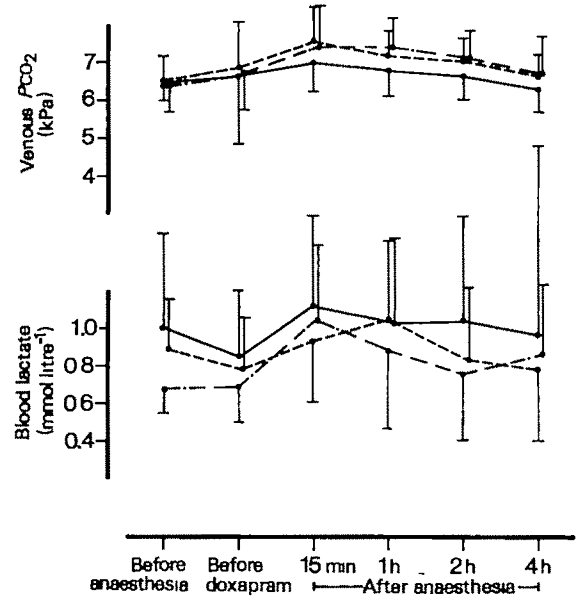

FIG. 2. Venous $P\text{CO}_2$ and blood lactate concentration (mean ± 1SD) in 20 MH susceptible (——), 19 MH non-susceptible (---) and five MH equivocal (·—·—·) patients before, during and after anaesthesia. No significant differences were found between the groups.

($P < 0.05$), and increased again after anaesthesia to reach the preanaesthetic value 4 h after anaesthesia (fig. 1).

In the MHS group, skin temperature did not change significantly during anaesthesia, but 4 h after anaesthesia a significant increase was seen. In the MHN group, skin temperature first decreased significantly, then increased again to a value which, 4 h after anaesthesia, was significantly greater than that before anaesthesia (fig. 1).

There were no significant differences between the groups in venous $P\text{CO}_2$ or blood lactate concentration at any time (fig. 2). Venous $P\text{CO}_2$ increased significantly in both the MHS and MHN groups 15 min after anaesthesia, then decreased again to achieve its preanaesthetic value 4 h after anaesthesia (fig. 2). There were no significant changes in blood lactate concentration in any of the groups (fig. 2).

DISCUSSION

All drugs administered to MH susceptible and MH non-susceptible patients were well tolerated. Specifically, no signs of incipient MH were noted in any of the 20 definite MH susceptible patients (95 % confidence limits 83–100 % (binomial distribution)).

Theoretically, vecuronium *per se* should not be a trigger of MH, since it is a pancuronium derivative without any sympathomimetic side effects [5], and pancuronium is usually considered safe in patients with MH [1]. However, vecuronium was tested by Buzello and colleagues [7] in eight MHS pigs, one of which developed overt MH during the infusion of vecuronium. The authors explained this triggering as a result of surgical stimulation—but without giving details. Their conclusion, that vecuronium is a non-triggering agent was, therefore, rightly questioned by Allen [6]. Our data support the view that vecuronium is safe in patients susceptible to MH. The observed discrepancy might well be explained by stress-induced and not vecuronium-induced triggering of MH in the pig: it is well known that MHS pigs are easily triggered by stress. However, more data—from the study of Buzello and colleagues—are necessary before such a conclusion may be drawn. Since the present study was ended, we have used vecuronium in another 24 MHS patients without any untoward effects (narrowing the 95 % confidence limits to 92–100 %). This, of course, does not prove that vecuronium is non-triggering, but does justify its clinical use in MHS patients.

Doxapram is used to reverse opioid-induced postoperative respiratory depression, because it does not antagonize analgesia [8]. In the present study doxapram was well tolerated in all patients, and there were no signs of an excess increase in muscle metabolism in the MHS patients (no difference in muscle temperature, blood lactate concentration or venous $P\mathrm{CO}_2$ between MHS and MHN patients).

Spontaneous ventilation was judged clinically to be sufficient in all patients at the end of anaesthesia. Venous $P\mathrm{CO}_2$, however, did increase significantly in the postoperative period, in spite of the administration of doxapram (fig. 2). Since neuromuscular blockade was monitored by train-of-four nerve stimulation throughout anaesthesia, antagonism was not attempted until it could be expected to be complete within a few minutes [16]. Furthermore, all patients were able to demonstrate a sustained head-lift for 10 s before being moved to the recovery room; residual curarization is, therefore, an unlikely explanation for the increase in $P\mathrm{CO}_2$. In addition, incipient MH can be excluded as cause of the increase in $P\mathrm{CO}_2$ since the increase was similar in MH susceptible and non-susceptible patients (fig. 2). The most likely cause of the increase in postoperative venous $P\mathrm{CO}_2$ was, we believe, a combination of an increase in metabolism as body temperature increased and respiratory depression following fentanyl. Since we did not measure arterial $P\mathrm{CO}_2$ or carbon dioxide production, we cannot assess the individual contributions of these two factors. However, doxapram had no ill effects in the MH susceptible patients, although, theoretically, it is a potential trigger of MH because of its ability to increase oxygen consumption [10].

As expected, rectal and muscle temperatures decreased significantly during anaesthesia and increased again following surgery. The measured values were similar in all groups during the whole of the study period (fig. 1) and were similar to those observed in a previous study of atracurium and neostigmine [4]. In contrast, significant differences between the groups were observed in skin temperature. We can offer no explanation for these differences which, however, were not consistent since one was in the MHN group and the other two in the MHE group (fig. 1). Since the decreases in rectal and muscle temperature were similar in the MHS and MHN groups, and skin temperature decreased only in the MHN group, total heat loss would have been expected to be greater in the MHN group. Such a difference was not reflected in postoperative temperatures, which were similar in these two groups. The MHE group was so small that further analysis of the increase in postoperative skin temperature in this group was not possible.

We have previously assessed the safety of antagonism of neuromuscular blockade with neostigmine in MH susceptible patients [4]. In this series, another 20 MHS patients received glycopyrrolate–neostigmine for antagonism of residual non-depolarizing neuromuscular block. In all, 59 MH susceptible patients, all monitored as described in the present paper, have received this combination and we have seen no signs of incipient MH in any patient—validating our previous conclusion that it is safe to antagonize neuromuscular blockade in MH susceptible patients, provided there are no signs of overt MH (giving new 95% confidence limits of 94–100% with the binomial distribution).

In conclusion, we found vecuronium to be a safe neuromuscular blocking agent for patients susceptible to malignant hyperthermia. A single injection of doxapram was without adverse effects in both MH susceptible and non-susceptible patients, but did not prevent an increase in postoperative venous $P\mathrm{CO}_2$.

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EVALUATION OF ATRACURIUM NEUROMUSCULAR BLOCKADE IN PAEDIATRIC PATIENTS WITH BURN INJURY

A. K. MILLS AND J. A. J. MARTYN

SUMMARY

The neuromuscular effects of atracurium were studied in acutely burned children, and in children at least 3 years after burn injury (controls). Thirty-one children were studied a total of 48 times. During nitrous oxide–narcotic anaesthesia, a single dose of atracurium was administered in each study and the twitch suppression recorded. Dose–response curves were established using least-squares regression techniques. The ED_{95} of atracurium in children recovered from burn injury was 0.27 mg kg^{-1}, which is similar to that of normal children reported previously. During the first week of burn injury, the ED_{95} was 0.3 mg kg^{-1} irrespective of burn size, and was not significantly different from controls. After the first week of injury, in children with 20–60% body surface burn, the ED_{95} was twice normal, while in those with greater than 60% body surface burn, it probably may be increased up to 3.0 mg kg^{-1}.

Depolarizing neuromuscular blocking drugs such as suxamethonium, can cause lethal hyperkalaemia when administered to burned patients [1, 2]. On the other hand, patients who have suffered thermal injury require increased doses of non-depolarizing myoneural blockers to achieve a given degree of neuromuscular blockade [2–5]. Atracurium is one such relatively new non-depolarizing neuromuscular blocking agent, which has a short to intermediate duration of action [6,7]. Its cardiovascular effects are minimal, even when large doses are administered—in contrast to the long-acting neuromuscular blockers such as tubocurarine and pancuronium [8–10]. Therefore, in clinical conditions such as burns in which suxamethonium is contraindicated [1], the use of atracurium may provide a suitable therapeutic alternative. The present study was performed to determine if children with burns exhibit resistance to the neuromuscular effects of atracurium; to study the relationship of resistance to time after burn and size of burn; and to construct dose–response curves for minor, moderate and major burns.

PATIENTS AND METHODS

Institutional approval was obtained from the Subcommittee on Human Studies, Committee on Research, and all studies conformed to ethical standards as delineated in the Declaration of Helsinki. Thirty-one children of either sex, ranging in age from 6 months to 17 years, were studied a total of 48 times. The mean age and weight of each group is given in table I.

The study patients were divided into five groups for purposes of analysis:

Group 1. Recovered burned patients coming for plastic reconstructive surgery (controls). These patients were injured at least 3 years before the study.

Group 2. Patients with acute burns who were studied within 7 days of injury. The mean (±SEM) size of burn in this group was 38 (±7)% (range 18–70%) total body surface area (TBSA).

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TABLE I. *Physical characteristics of patients studied. Values are expressed as mean ± SEM*

	Group 1	Group 2	Group 3	Group 4	Group 5
Burn size (% TBSA)	(0)	18–70	< 20	20–60	> 60
n	5	6	6	9	5
Age (yr)	9.6±0.9	6.6±0.8	7.0±0.9	4.1±0.4	9.2±0.6
Weight (kg)	30±3	22±2	23±2	17±1	28±2

Group 3. Patients with burns covering less than 20% TBSA (minor). The mean (±SEM) burn size of this group was 14 (±2)% TBSA.

Group 4. Patients with burns between 20% and 60% TBSA (moderate). The mean (±SEM) burn size of this group was 37 (±4)% TBSA.

Group 5. Patients with burns greater than 60% TBSA (major). The mean (±SEM) burn size of this group was 51 (±3)% TBSA.

Patients in groups 2–5 were studied at least 1 week after and up to 60 days after burn injury.

No patient had any serious medical problem, neuropathy or myopathy before sustaining their burn injury. There was no cardiac, hepatic or renal failure as indicated by clinical signs or laboratory tests—including measurements of the concentrations of SGOT, SGPT, BUN and creatinine. Patients were excluded from the study if they were receiving any drug known to alter the response to neuromuscular blocking drugs, and these included drugs such as antibiotics and theophylline [11, 12]. However, patients received cephalosporin and aminoglycoside antibiotics immediately after the termination of the study.

Premedication consisted of diazepam 0.05–0.20 mg kg^{-1} by mouth or morphine 0.10–0.15 mg kg^{-1} i.m. or i.v., or both drugs. The very young patients, in whom there was no venous access before the induction of anaesthesia, received methohexitone 20–25 mg kg^{-1} rectally. The ECG, arterial pressure, temperature and end-tidal carbon dioxide concentration (Hewlett–Packard) were monitored in each patient. Measurements of arterial pressure were obtained using the auscultatory method except in those patients who had indwelling arterial cannulae. Temperature was recorded by a telethermometer probe.

Anaesthesia was induced with thiopentone 4–6 mg kg^{-1} i.v. and 60% nitrous oxide in oxygen by mask. In infants with no venous access, halothane was always the anaesthetic of choice, given by mask for a short period (< 5 min) until a vein was cannulated; in these patients, studies were not commenced for a minimum of 10 min after the discontinuation of the halothane. It was assumed that this duration of exposure and wash out of halothane would not have any significant effects on dose–response curves to atracurium. Narcotic agents (morphine or fentanyl i.v.) were administered as anaesthetic supplements. Ventilation was controlled to maintain end-tidal carbon dioxide tension between 4.26 and 5.85 kPa.

After the induction of anaesthesia, the ulnar nerve was stimulated with a Grass S48 stimulator through 25-gauge needles inserted to a forearm which was immobilized on a padded board. The thumb was linked to a Grass FT03 force transducer, and the strength of contraction of the adductor pollicis was measured as twitch height on a Hewlett–Packard strip-chart recorder. Single square-wave stimuli of 0.15 ms duration were administered at 0.15 Hz.

Once a stable plane of anaesthesia, normal haemodynamic values and a constant twitch height were achieved and sustained for 5 min, atracurium was administered. The determination of ED_{50}, ED_{70} and ED_{95} was made by use of the "single-dose" technique described previously [13, 14] since the incremental dose technique results in artefactually larger estimates of ED values for drugs such as atracurium which have a rapid recovery time. Thus only one predetermined arbitrary dose was administered per patient and the resultant twitch depression was recorded. Twitch depression was measured as the difference between the control twitch height and the height of the twitch once it had stabilized after the dose of atracurium. Twitch height was considered to be stable when five twitches were of the same height. At this point, the study was terminated. Further doses of neuromuscular blocking drug were given if clinically indicated, but these doses were not taken into consideration for the calculation of ED values because of the uncertainty of how much atracurium had been metabolized from the initial dose.

Statistical analysis of the relationship between the percentage of twitch suppression and the logarithm of the dose was performed using a multiple regression model that provided a common slope for all groups and a separate intercept for each group. Combining the data in this way yielded more stable estimates of the common slope and of the residual variability. Graphical examination of the data revealed no evidence of systematic departure from straight-line dependence (within group) of twitch suppression on the logarithm of dose. Thus it was not necessary to transform the percentage of twitch suppression (for example to a probit scale). A more comprehensive multiple regression model, providing a separate slope for each group, permitted a test for the adequacy of the common-slope model; the difference between the two models was not significant ($P = 0.47$ for atracurium). Point estimates and 95 % confidence intervals for specified effective doses (e.g. ED_{50}) were obtained by a straightforward modification of the method described by Finney [15] for probit analysis.

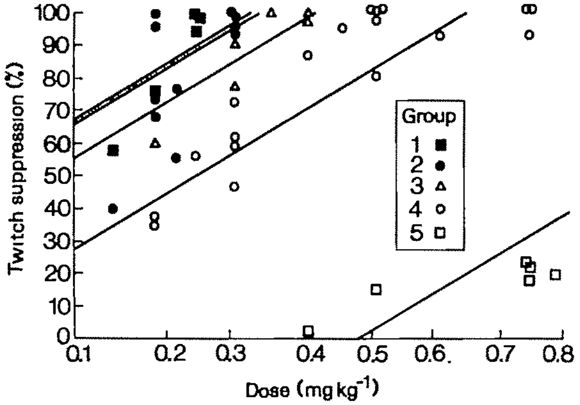

FIG. 1. Atracurium dose *v.* twitch depression in controls and acutely burned children. In the first week (●), the dose–response curves were similar to controls (■). After this time, there was a relative resistance to the effects of atracurium which was related to the size of the burn. The slopes of the curves are similar, but the intercepts are significantly different between minor (△), moderate (○) and major (□) burns. These groups were also significantly different ($P < 0.001$) when compared with controls and burned patients studied within 1 week of injury.

RESULTS

A plot of twitch suppression *v.* dose of atracurium for all groups is shown in figure 1. The ED_{50}, ED_{75}, and ED_{95} values for each group are shown in table II, together with the 95 % confidence limits for each ED value. It should be noted that the ED_{75} and ED_{95} values for group 5 were obtained by extrapolation beyond the data points. Patients in group 1 (controls) had a dose–response curve essentially the same as that reported previously for normal children [6]. Group 2 (those studied within 7 days of injury) demonstrated a dose–response curve that was not significantly different from the controls. In these patients there was no correlation between size of burn and ED values. The children in the other groups showed a relative resistance to the neuromuscular effects of atracurium, apparently related to the magnitude of the burn. Although the slopes were not different ($P = 0.43$), the intercepts of the minor, moderate and major burns were signifi-

TABLE II. *ED values of atracurium in burned children and controls. Numbers in parentheses represent lower and upper 95 % confidence limits, respectively.* †*Values obtained by extrapolation of line beyond data points.* ****Intercepts significantly different* ($P < 0.001$) *from each other and from groups 1 and 2*

	ED_{50}	ED_{75}	ED_{95}
Group 1	0.107	0.178	0.266
(Controls)	(0.083–0.132)	(0.145–0.0214)	(0.220–0.326)
Burns < 1 Week			
Group 2	0.0123	0.204	0.305
(18 %–70 % TBSA	(0.101–0.143)	(0.178–0.0231)	(0.268–0.354)
Burns > 1 Week			
Group 3	0.148	0.245	0.367***
(< 20 % TBSA)	(0.115–0.180)	(0.203–0.292)	(0.309–0.441)
Group 4	0.231	0.383	0.573***
(20–60 % TBSA)	(0.196–0.263)	(0.345–0.423)	(0.515–0.653)
Group 5	1.25	2.07†	3.093†***
(> 60 % TBSA)	(1.065–1.507)	(1.689–2.695)	(2.410–4.347)

cantly different ($P < 0.001$) from the controls, and from the burned patients studied within 7 days. The intercepts of minor, moderate and major burns were also significantly different from each other. There were no major changes in haemodynamic indices associated with the administration of atracurium. No injuries or complications resulted from the study.

DISCUSSION

This study has demonstrated that children with thermal injury are resistant (hyposensitive) to the effects of atracurium. This resistance was not observed in the first week after injury, irrespective of the area of the burn. After this period, however, resistance was observed, the magnitude of which was related to the size of burn. In other words, the greater the area of the burn, the greater were the ED values. Our study is consistent with another recent report indicating that burned patients are resistant to the neuromuscular effects of atracurium, and that this hyposensitivity does not develop until about 1 week after burn [5]. This latter study was performed in adults and did not establish ED values for twitch inhibition. Our study, therefore, adds to the previous work in that it was performed in children and establishes ED values for children with minor, moderate and severe burns.

The ED_{95} of 0.27 mg kg^{-1} in our control patients was similar to that reported for normal children (0.3 mg kg^{-1}) [6]. During the first week after burn, the ED_{95} was 0.3 mg kg^{-1}, a value not significantly different from that obtained in the control group. In group 2 there was no correlation between burn size and ED values. After the first week of injury the ED_{95} in patients with $< 20\%$ burn was shifted 1.2-fold (120%). The ED_{95} value for patients with 20–60% TBSA burns was approximately twice that of the control patients, while the ED_{95}, extrapolated beyond the data points (calculated), for patients with burns greater than 60% TBSA burns was almost 10 times that of control values. Such a resistance to the neuromuscular effects of atracurium has not been seen in any other clinical pathological state. A combination of factors might account for this significant shift to the right in the dose–response curve for atracurium. These factors include altered kinetics [16], altered protein binding [17, 18] and, possibly, the presence of circulating substances in the plasma [19, 20]. Altered kinetics which might influence dose include changes in central volume of distribution and 24-h urinary excretion [16]. Enhanced drug binding to plasma is brought about by increases in alpha$_1$-acid glycoprotein [17, 18]. Circulating factors which may shift the dose–response curve to the right include changes in the concentrations of cyclic nucleotides, prostaglandins and other unidentified substances [11, 19, 20]. More importantly, there seems to be a generalized increase in the number of nicotinic acetylcholine receptors in all skeletal muscles following burn injury [21]. Therefore, the changes in acetylcholine receptors at the skeletal muscle following burns are akin to the changes seen following denervation [1]. Clinically, electromyographic studies in burned patients also confirm the presence of a denervation-like state which includes positive sharp waves and fibrillation potentials [22]. Such a change in target organ sensitivity could account for the aberrant responses to both suxamethonium and the non-depolarizing drugs [2].

An important advantage of atracurium is its short duration of action and minimal cardiovascular effects compared with tubocurarine, dimethyl-tubocurarine and pancuronium. A good substitute for suxamethonium for use in emergency situations such as a "full stomach" or in laryngospasm is presently not available for use in burned patients [2]. High doses of pancuronium and metocurine administered together produce rapid onset of paralysis, but the time to recovery to 25% of control twitch height is greater than 80 min [23]. High-dose atracurium may prove useful as a substitute for suxamethonium in these emergency situations. A dose of atracurium 1.5 mg kg^{-1} ($6 \times ED_{95}$ in normal individuals) has been administered to normal patients and 95% twitch depression was achieved in approximately 60 s [9]. This was associated with a decrease in arterial pressure of only 22 ± 15 (mean ± SD) mm Hg. Although arterial pressure was not monitored in a systematic, timed fashion, we did not observe any clinically significant decrease in our patients when high doses were administered. A recent study, in adult burned patients, confirms that high-dose atracurium does not cause significant hypotension [24]. These authors, however, used only 0.8 mg kg^{-1} in both burned and unburned patients. A 20% decrease in arterial pressure was seen in the normal patients whereas, in burned patients, a

5% decrease was observed. The reason for the absence of significant hypotension in burned patients is subject to speculation. Clinical study with larger doses ($> 1.5\ \mathrm{mg\ kg^{-1}}$) to evaluate onset times and haemodynamic changes is warranted, since atracurium $0.8\ \mathrm{mg\ kg^{-1}}$ will not cause as rapid an onset of paralysis in burned patients as suxamethonium. High-dose vecuronium may also prove useful [25].

In burns, another theoretical advantage of atracurium over other presently available non-depolarizing neuromuscular blocking drugs is its lack of dependence on the kidney or liver for breakdown [26]. Furthermore, the metabolic breakdown products of atracurium have no effect on the neuromuscular junction. Thus, when burned patients have impaired renal or hepatic function, atracurium may be superior to other drugs. On the other hand, burned patients have altered kinetics of almost every drug studied [4]. Serum concentrations of specific and non-specific esterases are depressed [27, 28]. The effects of these alterations in enzyme concentrations on the pharmacokinetics of atracurium in burned patients need to be clarified in future studies.

This study has established dose–response curves for burned paediatric patients, and confirmed those for normal patients. Most thermally injured patients do show relative resistance to atracurium, and the degree of resistance appears to be related to extent of burn and the time after the injury. The ED_{95} for control subjects is $0.27\ \mathrm{mg\ kg^{-1}}$ and is not significantly different from the ED_{95} of burned patients studied within 1 week of injury, irrespective of burn size. In patients with moderate burns, the ED_{95} is twice normal, while in patients with major burns it may be increased up to 10-fold ($3.0\ \mathrm{mg\ kg^{-1}}$). The pharmacokinetics and the cardiovascular and neuromuscular pharmacodynamics of high-dose atracurium as a substitute for suxamethonium in burned patients deserve further study.

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VENTILATORY EFFECTS OF OXYGEN IN THE DOG UNDER THIOPENTONE ANAESTHESIA

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SUMMARY

The ventilatory effects of prolonged oxygen administration were examined in seven dogs during thiopentone anaesthesia. Ventilation, tidal volume (V_T), ventilatory rate (f), minute ventilation (V_E), inspiratory time (T_I), expiratory time (T_E), period (T^{tot}), T_I/T^{tot} and mean inspiratory flow (V_T/T_I) were measured during the inhalation of room air, after 30 min of oxygen inhalation, and finally after a return to breathing room air. Arterial blood-gas tensions were measured before and after 5, 10, 20 and 30 min of oxygen administration and 15 min after return to breathing room air. Oxygen administration produced an immediate, significant and persistent decrease in ventilation, principally from a decrease in ventilatory rate and changes in ventilatory times. This was in contrast to what occurred in awake animals. Modifications in ventilatory mechanics or suppression of an hypoxic stimulus to ventilation were probably not involved. Anaesthesia may modify centrally mediated ventilatory responses to hyperoxia.

General anaesthesia profoundly disturbs the ventilatory and respiratory systems. Ventilatory mechanics and gas exchange are modified [1] as is ventilatory control. For instance, the Breuer–Hering reflex [2] is difficult to elicit in the awake human or animal, but is easily demonstrated in the anaesthetized animal [3] and man [3, 4]. Ventilatory response to chemical stimuli, to carbon dioxide [5], to metabolic acidosis [6] and to hypoxia [7–10] are diminished. Numerous studies have been undertaken on the effects of hyperoxia on ventilation in the awake or anaesthetized man or animal, but the conclusions, particularly regarding prolonged administration of oxygen, remain controversial.

Gaudy and colleagues [11, 12], using dogs anaesthetized with alphaxalone–alphadolone confirmed earlier studies by Mosso [13] and Marshall and Rosenfeld [14] which showed that hyperoxia induces marked respiratory depression in the anaesthetized animal, whether the animals were initially hypoxaemic or not. The response to hyperoxia may differ when other i.v. anaesthetics are used. Indeed, the response to hyperoxia varies according to the anaesthetic agent administered, and in the case of alphaxalone–alphadolone the results observed in the dog may partly result from histamine release induced by Cremophor EL, the solvent for the two steroids. The purpose of the present study was to examine the ventilatory effects of hyperoxia in dogs under thiopentone anaesthesia.

MATERIAL AND METHODS

The study was performed in seven male beagle dogs (mean body weight ± SD = 23.1 ± 3.3 kg). Anaesthesia was induced with thiopentone 0.25 g i.v. and maintained with thiopentone 4 g diluted in 500 ml of saline administered by means of an electric pump (0.29 ± 0.08 mg kg^{-1} min^{-1}). After induction of anaesthesia the trachea was intubated and an airtight seal was obtained. In order to minimize ventilatory resistance, the tracheal tube was attached to a T-shaped tube. One of the side extensions was connected to a Douglas bag (5 litre) which was supplied with either air or oxygen ($FI_{O_2} = 1.00$). The other side of the T-shaped tube was left open. The flow of gases was adjusted to be markedly greater than inspiratory flow. Rectal temperature was maintained at 38 °C ± 0.5 by means of a thermostatically controlled heating

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TABLE I. *pHa, blood-gas tensions* (Pa_{CO_2}, Pa_{O_2}) *and ventilatory parameters (minute ventilation,* $\dot{V}E$; *tidal volume,* VT; *frequency* f; *inspiratory time,* TI; *expiratory time,* TE; *duration of cycle,* T^{tot}; *ratio* TI/T^{tot}; *and inspiratory flow,* VT/TI) *during air breathing, before oxygen administration (mean ± SD)*

Time (min)	pHa	Pa_{CO_2} (kPa)	Pa_{O_2} (kPa)	$\dot{V}E$ (litre min^{-1})	VT (ml)	f (b.p.m.)	TI (s)	TE (s)	T^{tot} (s)	TI/T^{tot}	VT/TI (ml s^{-1})
0	7.27	7.74	11.74	5.67	171.6	36.5	0.67	1.51	2.18	0.34	271.4
	0.04	0.51	1.35	2.22	38.0	21.0	0.22	1.04	1.23	0.08	62.7
5	7.27	7.57	12.08	5.59	172.4	35.3	0.68	1.55	2.23	0.34	270.2
	0.03	0.28	1.25	2.03	35.0	20.3	0.22	0.95	1.23	0.08	71.1
15	7.27	7.45	12.47	5.37	187.6	31.9	0.71	1.70	2.41	0.32	275.2
	0.04	0.03	1.33	1.87	45.1	18.4	0.22	0.97	1.16	0.07	56.5

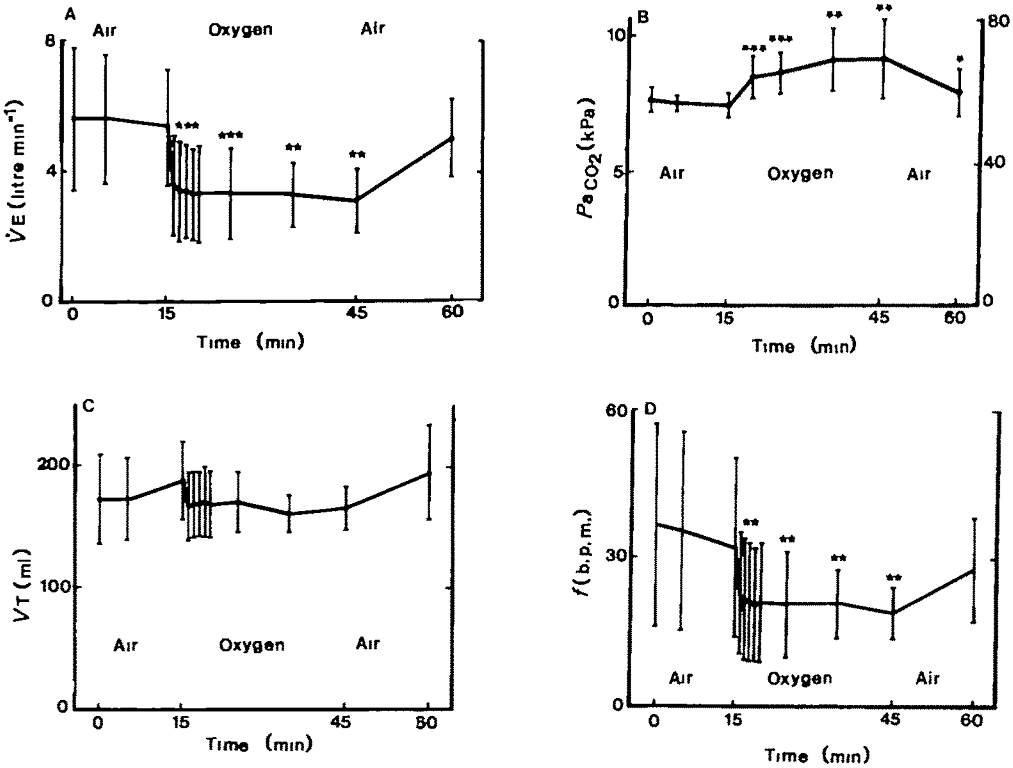

FIG. 1. Effects (means ± SD) of oxygen breathing on: A, minute ventilation ($\dot{V}E$) (ml min^{-1}); B, arterial PCO_2 (mm Hg and kPa); C, tidal volume (VT) (ml); D, ventilatory rate (f) (b.p.m.). $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

pad. A catheter was placed in a femoral artery for measurement of arterial pressure (using a Statham P23IA transducer) and for collection of blood samples for the determination of pHa, Pa_{CO_2}, Pa_{O_2}. Blood-gases were measured within 2 min of sampling (Instrument Laboratories model 313). The concentration of carbon dioxide in the expired gases (FCO_2) was also monitored continuously (Beckman LB2). The spirogram was obtained after integration of the pneumotachograph signal (Fleish No. 2, Statham transducer). Calibration of the pneumotachograph was performed at the beginning and end of each experiment with each of the two gases (air and oxygen). The pneumotachograph signal (flow, $\dot{V}$, and tidal volume, VT) was recorded on a polygraph (Beckman Dynograph R 411) at a speed of 25 mm s^{-1}.

Each study commenced after 30 min at steady

TABLE II. *Effects of oxygen breathing upon ventilation times (mean ± SD).* T*I* = *inspiratory time*; T*E* = *expiratory time*; T^{tot} = *duration of cycle. Significant differences from initial values breathing air*: $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$

		Oxygen								
	Air	1 min	2 min	3 min	4 min	5 min	10 min	20 min	30 min	Air
*T*I (s)	0.71	0.82	0.89**	0.88***	0.87***	0.88**	0.89**	0.91**	0.93**	0.75
	0.22	0.20	0.26	0.24	0.23	0.24	0.22	0.16	0.16	0.21
*T*E (s)	1.70	2.49*	2.75*	2.70*	2.88**	2.83*	2.94*	2.25**	2.42***	1.73
	0.97	1.49	1.68	1.69	1.74	1.74	2.23	0.93	0.89	0.92
T^{tot} (s)	2.41	3.31*	3.64*	3.58**	3.75***	3.71**	3.90*	3.16**	3.55***	2.48
	1.16	1.66	1.91	1.89	1.92	1.93	2.32	1.04	0.94	0.87
T_I/T^{tot}	0.32	0.28*	0.28*	0.28**	0.26***	0.27**	0.27**	0.30*	0.29*	0.32
	0.07	0.08	0.08	0.08	0.08	0.08	0.08	0.07	0.08	0.08

state (end-tidal carbon dioxide, ventilatory rate, *f*, tidal volume and temperature) with the dogs breathing air. Air was then replaced by 100% oxygen for 30 min, after which the dogs again breathed air. Arterial blood-gas tensions were measured before administration of oxygen, at 5, 10, 20 and 30 min of oxygen inhalation, and 15 min after return to air breathing. The spirogram was recorded for 1 min before these measurements, and continuously during the first 5 min of inhalation of oxygen. Tidal volume (*V*T), duration of inspiration (*T*I), duration of expiration (*T*E), and duration of the breathing cycle (T^{tot}) were measured. For *V*T, *T*I, *T*E and T^{tot} the average value was calculated from groups of eight successive cycles. Ventilatory rate ($60/T^{tot}$ s^{-1}), minute ventilation ($\dot{V}_E = V_T \times f$), the ratio T_I/T^{tot} and mean inspiratory flow (*V*T/*T*I) were calculated. For analysis of the data, one way analysis of variance and Student's *t* test on paired series were used.

RESULTS

Preliminary, steady-state values for the parameters studied are presented in table I.

Inhalation of oxygen increased mean Pa_{O_2} from 12.42 kPa to 60.75 kPa and induced a marked and significant decrease in ventilation. This decrease was immediate (−33.5% after 1 min) and sustained (−42% after 30 min) (fig. 1A). Pa_{CO_2} increased significantly during the inhalation of oxygen (fig. 1B). Tidal volume did not change significantly (fig. 1C) and the decrease in ventilation was mainly a result of a decrease in ventilatory rate (fig. 1D).

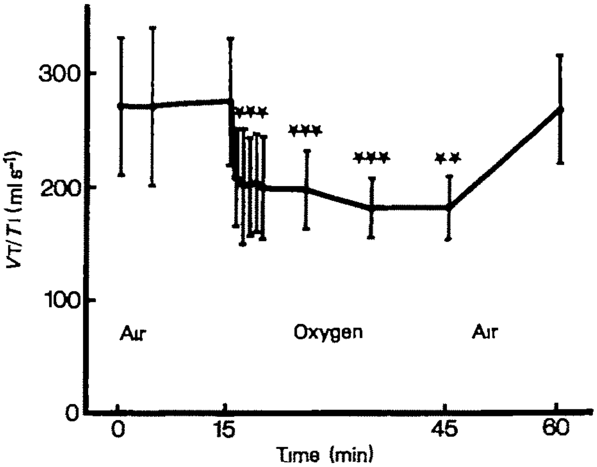

FIG. 2. Effects (mean ± SD) of oxygen breathing on mean inspiratory flow (*V*T/*T*I) (ml s^{-1}). $^{**}P < 0.01$; $^{***}P < 0.001$.

Ventilatory timing was significantly modified: T^{tot}, *T*I and *T*E increased, and T_I/T^{tot} decreased (table II). Mean inspiratory flow (*V*T/*T*I) decreased immediately after administration of oxygen and this decrease was sustained (fig. 2). After 15 min inhalation of room air, all values returned to basal values and, with the exception of Pa_{CO_2}, did not differ significantly from these basal values. Systemic arterial pressure and heart rate did not change significantly.

DISCUSSION

The results of this study show that, in the dog during thiopentone anaesthesia, administration of oxygen induced an immediate and sustained decrease in ventilation that was related essentially to a decrease in ventilatory rate. These effects of oxygen differ markedly from those observed in the awake animal and man. In man, immediate and transient hypoventilation has been observed [15–17] after brief exposure (up to 1 min) to hyperoxia. Identical results have been noted in the awake dog [18]. With prolonged exposure (5–20 min), either no change or mild hyperventilation has been observed [15, 17, 19–21]. The immediate decrease in ventilation has been attributed to a sudden change in the peripheral chemoreceptor stimulus to ventilation. The subsequent increase in ventilation toward or exceeding control values has been explained less satisfactorily. Several factors, including modifications in blood chemistry and cerebral flow [22] have been implicated, although not fully documented [23]. However, the results of the present study show that general anaesthesia profoundly modifies the response to hyperoxia, thus confirming the earlier studies of Mosso [13] and Marshall and Rosenfeld [14].

The ventilatory decrease induced by oxygen in the anaesthetized dog may result from various mechanisms: changes in arterial pressure, depth of anaesthesia and ventilatory mechanics, and effects on central ventilatory control. The observed respiratory changes cannot be explained by an influence of baroreceptor activity on respiratory control [24], since arterial pressure and heart rate did not vary significantly when air was changed to oxygen breathing.

The ventilatory effects of oxygen breathing were similar to the changes in ventilation observed in the dog under thiopentone anaesthesia when anaesthesia is deepened: namely, a decrease in ventilation produced essentially by a decrease in ventilatory rate [25]. However, our results are unlikely to be caused by variation in the level of anaesthesia (deepening or lightening), since there was no significant difference in respiratory parameters (with the exception of Pa_{CO_2}), between air breathing before and after exposure to oxygen. The fact that Pa_{CO_2} was slightly greater than that before administration of oxygen can be explained on the basis that the period of air breathing with the return to base-line ventilation was short compared with the period of oxygen inhalation (15 and 30 min, respectively) and this did not permit elimination of the carbon dioxide accumulated during the 30 min of oxygen-induced hypoventilation.

Hyperoxia may affect ventilatory control through various mechanisms: (1) peripheral effects caused by a decrease in arterial chemoreceptor activity; (2) central effects which result in an increase in breathing caused by suppression of control inhibition [21], and (3) mixed or indirect effects which may interfere with the control of breathing, cerebral blood flow [22] and central acid–base disturbances [26]. All three mechanisms may be modified by thiopentone. The suppression of the hypoxic stimulus to ventilation by oxygen breathing is possible, but unlikely. Before administration of oxygen, the animals were mildly hypoxaemic ($Pa_{O_2} = 12.47 \pm 1.33$ kPa) and hypercapnic, which can be explained by the decrease in alveolar ventilation and venous admixture induced by anaesthesia [27]. Hypoxaemia during air breathing was too moderate to stimulate ventilation so that administration of oxygen would decrease ventilation to 30–40% of that in air. Most importantly, it is well known that anaesthetics, and in particular barbiturates [8, 10], depress the ventilatory response to hypoxia. The sustained nature of the ventilatory depression produced by oxygen, despite significant hypercapnia, may be explained in part by the fact that anaesthesia diminishes the ventilatory response to carbon dioxide [5] and that this response is also diminished by hyperoxia [28]. Therefore, direct or indirect action on the central mechanisms of ventilatory control, especially those regulating ventilatory times, cannot be excluded.

The effects of hyperoxia on ventilatory times during thiopentone anaesthesia have not been described previously. The immediate and sustained changes after oxygen administration in this study were essentially an increase in both T_I and T_E and a decrease in V_T/T_I, the latter linked to an increase in T_I. These changes in ventilatory times may result from changes in the mechanical properties of the ventilatory system or in the timing mechanisms of ventilation. The results of the present study do not explain the mechanisms of the ventilatory depression and modification in ventilatory times produced by oxygen in the thiopentone-anaesthetized dog. A study of the effects of hyperoxia in intact, chemically denervated (to study the role of the peripheral chemoreceptors), vagotomized (to study the role of the Breuer–Hering reflex), and decerebrate (to study the role of central structures), awake and thiopentone-anaesthetized animals is needed. Nevertheless, an action of oxygen on central mechanisms of ventilatory control is very likely. Recently, Gautier, Bonora and Gaudy [29], studying conscious intact, carotid denervated, and lightly or deeply anaesthetized cats, suggested that oxygen may centrally stimulate breathing and offset the decreased input from the peripheral chemoreceptors during hyperoxia in the conscious or lightly anaesthetized animal; this mechanism, very sensitive to anaesthesia, could explain the permanent decrease in ventilation when oxygen is given during deep anaesthesia, which may suppress this central action of oxygen.

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CONTRALATERAL HAEMOTHORAX: A LATE COMPLICATION OF SUBCLAVIAN VEIN CANNULATION

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SUMMARY

Contralateral haemothorax developed as a late complication of subclavian vein cannulation following gradual erosion of the wall of the superior vena cava by the tip of the catheter. The use of a relatively rigid catheter and a left-sided approach may have contributed to this rare, but potentially fatal complication.

Since its introduction, subclavian vein cannulation [1] has gained popularity. Critically ill patients in Intensive Care Units (ICU) need long-term venous access for parenteral nutrition, haemodynamic monitoring and haemofiltration.

Laceration of the subclavian or innominate vein by a central venous catheter or its introducing device, often results in life-threatening complications. The occurrence of mediastinal haematoma or haemothorax, although rare, can be recognized readily and reduced to an acceptable frequency by fixed policy, meticulous technique and supervision [2–4]. However, late complications may be difficult to recognize and contralateral manifestations may compound diagnostic difficulties. The following case report highlights such a problem.

CASE HISTORY

A 69-year-old woman was admitted to the ICU following laparotomy for drainage of a splenic abscess and peritonitis. She was suffering from septicaemia, and renal and respiratory failure. She was established on IPPV and antibiotic therapy commenced. It was decided to treat her renal failure with haemofiltration. A dual-lumen polyurethane central venous catheter (Vaccess 4000, VasCath, Canada) was inserted via the *left* subclavian vein using an infraclavicular approach. Although the patient's condition was aggravated by multiorgan failure in addition to diabetes mellitus, she made a good recovery in the early postoperative period.

On the 5th day after operation she developed intestinal bleeding for which a left hemicolectomy was performed. Two days later her cardiovascular system became unstable. A flow-directed pulmonary artery catheter was inserted via the *right* subclavian vein for haemodynamic monitoring. A day later, a right pleural effusion appeared on chest x-ray, for which a chest drain was inserted. Three litre of blood was drained from the right thoracic cavity. It was thought that the haemothorax was caused by, or during, insertion of the flow-directed catheter, although the position of the catheter was previously confirmed by radiography. The patient was treated conservatively. Cardiovascular stability was restored after she was given 12 units of blood. At that time, however, her renal function recovered and the left subclavian dual lumen catheter was used only for administering parenteral nutrition and drugs. Blood sugar concentration, however, was persistently increased (greater than 30 mmol litre^{-1}) despite large i.v. insulin increments and her high arterial pressure failed to respond to sedatives and hypotensive drug therapy. Although the bleeding stopped within 24 h, a considerable amount of fluid (3–5 litre day^{-1}), similar in appearance to her parenteral feed, was draining from the right pleural cavity. This fluid was later analysed and found to have a high glucose content (130 mmol) litre^{-1}).

Finally, it was noted that the patient did not respond to methohexitone and suxamethonium

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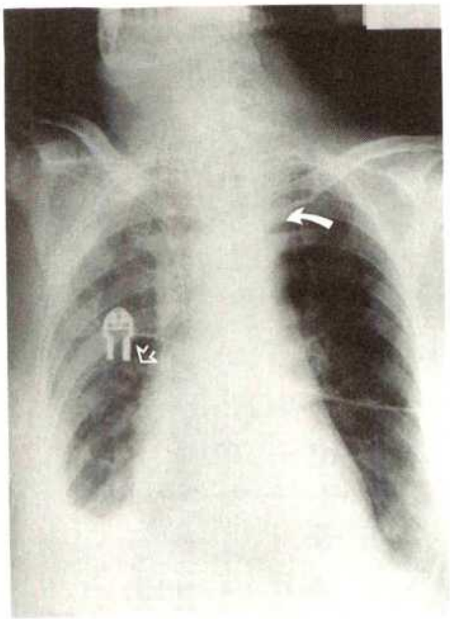

FIG. 1. Chest radiograph showing the tip of the dual-lumen catheter (open arrow) in the pleural cavity.

when they were administered via the same catheter to facilitate the change of her tracheal tube. The Vaccess catheter was, therefore, suspected to have eroded the wall of the superior vena cava (SVC). Injection of contrast media followed by a radiograph confirmed that the tip of the catheter was lying in the right pleural cavity (fig. 1).

Infusions via the catheter were discontinued; the lumina were filled with tetracycline and the injection ports were capped. Three days later it was withdrawn without further complication. Unfortunately, the patient died 1 month later, from septicaemia and cardiac failure. No other sign of mediastinal complications was found at autopsy.

DISCUSSION

Ipsilateral pulmonary complications following subclavian vein cannulation are well documented [2, 4]. Contralateral haemothorax caused by guide wires is rare and manifests itself soon after the cannulation procedure [5–7]. Delayed perforation of the vessel wall is associated with a high incidence of hydrothorax, in contrast to haemothorax [8, 9]. Diagnosis and treatment of this complication is often delayed [8]. Although lateral chest radiographs were not taken, periodic radiography indicated satisfactory position of both Vaccess and flow-directed catheters. Furthermore, haemofiltration and haemodynamic measurements were carried out successfully for 8 days and 1 day via each catheter, respectively.

The appearance of haemothorax following right subclavian vein cannulation made the diagnosis difficult. The tip of the Vaccess catheter was suspected to lie outside the superior vena cava when the patient failed to respond to anaesthetic drugs and fluid resembling chyle was recovered from the right chest. Chest radiographs showing satisfactory positioning of a central venous catheter within the vein appears to be no guarantee against its secondary migration. It may also be possible to aspirate blood from a multi-lumen catheter even though its tip is no longer within the vessel [2, 9]. Secondary migration of unsecured catheters may occur during cardiorespiratory motion. This may be sufficient to cause erosion of the vessel wall [2, 10, 11].

Chest radiographs of this patient (fig. 1) in addition to other patients (fig. 2) whose central veins were cannulated by similar catheters were reviewed. Because of the horizontal orientation of the left brachiocephalic vein and its 90° junction with the SVC, left subclavian vein cannulation allows the catheter to acquire a transverse course. This course tends to bring the catheter tip in opposition against the vessel wall and increases the risk of erosion of the vessel wall. In eight out of nine reported SVC perforations [9] the catheter was inserted on the left side. Furthermore, the appearance of a gentle curve at the tip of

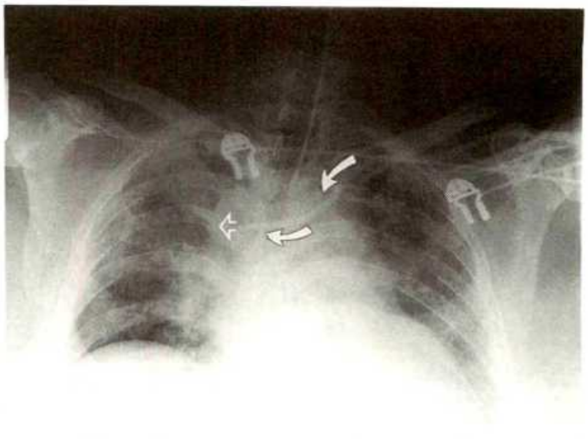

FIG. 2. Chest radiograph showing the curve taken by catheter (closed arrows) inserted from the left side and its tip (open arrow).

the catheter was claimed to be a radiographic sign of threatening perforation.

Soft catheters with blunt tips have reduced the frequency of vascular perforation [12, 13]. However, the use of relatively rigid catheters such as those for temporary haemofiltration are likely to increase this hazard. The large diameter of dual-lumen catheters (14-gauge) may cause a sizeable tear in the vessel wall. It may cause severe haemorrhage at the time of perforation, as in the present patient, or upon withdrawal of the catheter.

This case history illustrates a potential hazard of the increasing use of relatively rigid dual-lumen haemofiltration catheters. However, their use remains valuable in the management of ICU patients who are in renal failure. Whenever possible, these catheters should not be inserted via the left subclavian vein. Unexplained pleural effusion of high glucose content or resistance to drugs administered via the catheter should immediately raise the suspicion of vein perforation. Perforation may be prevented by catheter withdrawal if a gentle curve of its tip is recognized during periodic chest radiography, particularly in lateral views. All lumina of a multilumen catheter must be checked to ensure its appropriate position.

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ANAESTHESIA FOR TRANSSPHENOIDAL SURGERY IN A PATIENT WITH EXTREME GIGANTISM

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SUMMARY

The management of anaesthesia for transsphenoidal removal of a pituitary adenoma in a true pituitary giant with acromegaly is described. Problems which may be anticipated in such a patient and an approach to their management are discussed, with particular emphasis upon the need for thorough preoperative assessment of the upper airway and the provision of adequate pulmonary ventilation during anaesthesia.

True gigantism is a rare endocrine disorder caused by the excessive secretion of growth hormone from an anterior pituitary tumour before pubertal closure of the epiphyses. This results in exaggerated yet proportional bone growth, unlike acromegaly which has the same origin but occurs after puberty and is associated with disproportionate enlargement of the face and acral parts of the hands and feet. Treatment, whether medical or surgical, is aimed at restoring the production of growth hormone to normal so as to curb the progressive organ and soft tissue hypertrophy.

Although the anaesthetic management of acromegalic patients has been reviewed from a number of perspectives [1, 2], there has been no previous description of experience with pituitary giants. This case report illustrates some unique anaesthetic problems relevant to such a patient undergoing transsphenoidal surgery for the removal of a pituitary adenoma.

CASE REPORT

The patient was a 29-yr-old female with an established diagnosis of gigantism. Excessive growth had been noted at age 3 yr, and by the time she was 12 years old, she was more than 6 ft (1.80 m) tall. Treatment was declined until she was aged 22 yr and more than 7 ft (2.10 m) tall in stature when, at another centre, craniotomy to remove a pituitary adenoma was carried out. Seven years later, recurrence of an increase in growth hormone concentration brought her to this hospital for surgical intervention in an attempt to curb the progression of acromegalic disease.

Records available pertaining to the first operation indicated that general anaesthesia was uneventful. Previous surgery also included two knee operations in the remote past, and thyroidectomy 3 yr before the current admission. Although tracheal intubation had been performed without incident in all procedures, difficulty in maintaining optimal ventilation was encountered throughout the thyroid surgery using manually assisted ventilation with a Mapleson D (Bain) system, and episodes of ventricular bigeminy had occurred in association with hypercarbia.

Other relevant history indicated that she smoked 45 cigarettes daily. She had severely limited exercise tolerance attributable to her enormous body mass and osteoarthritis affecting her knees and lumbar spine. She had no symptoms of upper airway obstruction. Current hormone replacement consisted of thyroxine and cortisone acetate, and bromocriptine was being given to suppress the production of growth hormone.

On physical examination the patient was extremely large, measuring 232 cm (7 ft 7.25 in) in height and weighing 186 kg (410 lb). She occupied three hospital beds pushed together in a two-

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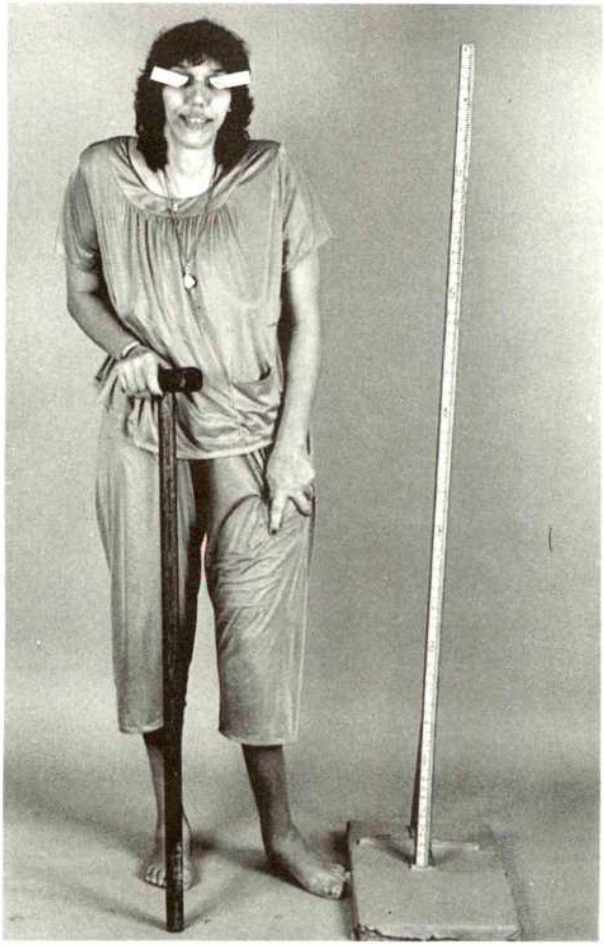

FIG. 1. The patient. Note the coarse facial features, prognathism and enlarged extremities.

patient room. The classical stigmata of advanced acromegaly were evident (fig. 1).

Respiratory and cardiovascular systems were normal clinically. Examination of the upper airway showed macroglossia, with some hypertrophy of the oral mucosa. Temporo–mandibular and neck mobility were normal, these findings being no different from those observed 3 yr previously. Haematocrit, chest x-ray and arterial blood-gas tensions were normal. Her tidal and minute volumes were 1.3 litre and 12.5 litre, respectively, with a total lung volume of 16.6 litre. Further spirometric studies showed FEV$_1$/FVC to be 54% and moderate airflow reduction at low lung volumes. The flow–volume curve showed normal maximum inspiratory and expiratory flow rates with no evidence of extrathoracic upper airway obstruction. Endocrine studies demonstrated an increased serum growth hormone concentration of 30 ng ml^{-1} (normal $<$ 10 ng ml^{-1}) and a deficient cortisol response to insulin-induced hypoglycaemia. Computerized axial tomogram indicated no extrasellar extension of the pituitary tumour.

Preoperative preparation included chest physiotherapy and salbutamol by inhalation. The only immediate preoperative premedication was hydrocortisone succinate 100 mg i.v. Upon arrival in the operating room the patient was able to transfer herself to a specially reconstructed operating table.

After pre-oxygenation, and precurarization with pancuronium 1.5 mg, anaesthesia was induced with thiopentone given slowly i.v. until loss of eyelid reflex (700 mg) and suxamethonium 200 mg (1 mg kg^{-1}) was administered to facilitate intubation of the trachea. Upon direct laryngoscopy with a No. 4 MacIntosh blade, the pharynx and epiglottis were easily visualized, but the glottic opening was not seen because of its extreme inferior and anterior position. Intubation of the trachea with a No. 8 armoured tube was accomplished by blind per-oral insertion, during which supplementary thiopentone and suxamethonium were given. Anaesthesia was maintained with nitrous oxide and enflurane in oxygen; fentanyl and pancuronium were given i.v. as required. Ventilation was controlled using an Airshields Ventimeter ventilator, delivering a tidal volume of 1.3 litre, 12 b.p.m. (a total minute volume of 16 litre min^{-1}) via a circle system. A total fresh gas flow of 14 litre min^{-1} of nitrous oxide and oxygen with an $F\text{I}_{O_2}$ of 0.4, maintained intra-operative Pa_{CO_2} at 4 kPa (30 mm Hg) and Pa_{O_2} at 18.7 kPa (140 mm Hg). Monitoring included end-tidal $P\text{E}_{CO_2}$, direct measurements of arterial and central venous pressures, peripheral nerve stimulator and Foley catheter.

Selective transsphenoidal resection of an anterior pituitary adenoma was accomplished in 6 h. After surgery the trachea was extubated in the operating room, and after 48 h of observation in the recovery room, the patient was transferred to the surgical ward where she subsequently made an uneventful recovery.

DISCUSSION

In a patient such as this, a number of difficulties may be anticipated by the anaesthetist. Difficulty in airway management as a result of increased

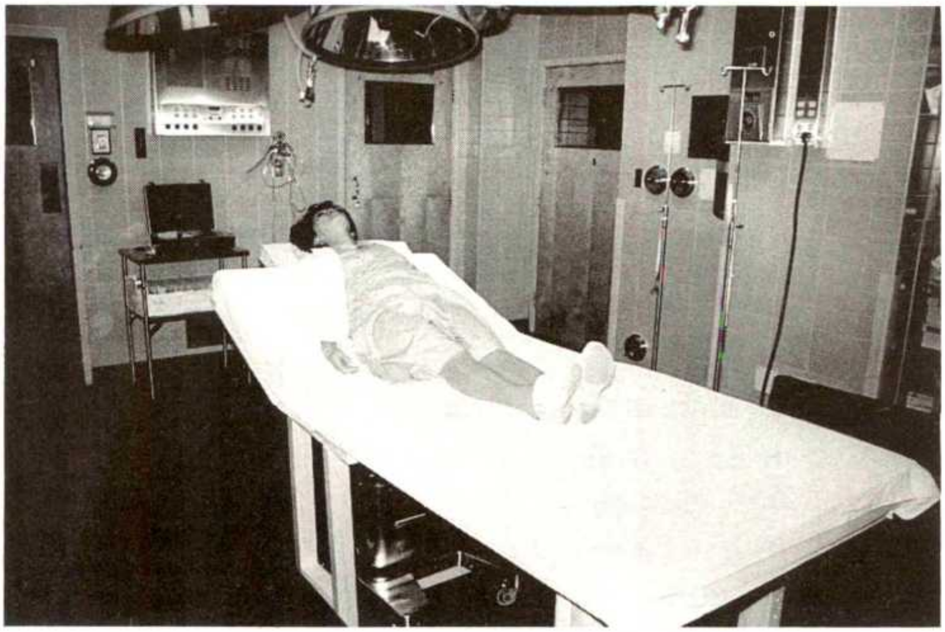

FIG. 2. Modified operating table with average subject.

length of the hypopharynx and encroachment of pharyngeal and laryngeal mucosa in the acromegalic patient has been well recognized since 1896 [3]. Messick, Cucchiara and Faust [4] studied 94 patients, in 39 of whom there was difficulty in intubation: either visualization of the glottic opening was obscured by hypertrophic oral, pharyngeal and laryngeal soft tissue, or there was glottic stenosis or distortion. Airway obstruction from thyroid enlargement may also occur [5]. Southwick and Katz [6] defined four grades of airway involvement:

(1) No involvement
(2) Nasal or pharyngeal mucosal hypertrophy
(3) Glottic stenosis
(4) Combination of 2 and 3.

Elective tracheotomy was recommended for grade 3 and 4 patients, but other authors [7] have suggested that fibreoptic laryngoscopy with orotracheal intubation is a safe alternative.

Pre-anaesthetic assessment should note any symptoms and signs of airway involvement such as exertional dyspnoea, hoarseness, stridor, macroglossia or oropharyngeal mucosal hypertrophy. More objective assessment by indirect laryngoscopy, soft tissue x-rays of the neck [8] and inspiratory and expiratory flow-volume studies may be helpful [9]. Our patient had a mild degree of macroglossia, and some hypertrophy of the oral mucosa, with no observable changes in facial features or respiratory function since her last surgery; serious airway problems were, therefore, not anticipated.

Once a secure airway has been established, maintenance of adequate respiratory exchange should not normally pose a special problem in the acromegalic patient. However, in this case of gigantism, enormous respiratory volumes were required in order to maintain Pa_{CO_2} at recommended values [10], and the need for specially adapted ventilatory equipment was considered.

Other problems which may be encountered in the acromegalic patient are hypertension, an idiopathic cardiomyopathy [11, 12] and diabetes mellitus; no evidence of these were found in this patient. Increased intracranial pressure may occur in the presence of extrasellar extension of the tumour, in which case volatile anaesthetic agents should be used with caution [4]. In this case there was no evidence of increased intracranial pressure and enflurane was used without incident. Sleep apnoea is also a recognized complication [13], daytime somnolence and excessive snoring being suggestive of the diagnosis. In such patients there is risk of postoperative hypoxaemia when the residual effects of the general anaesthetic agent may depress central nervous system arousal centres, obtund airway reflexes and delay secretion

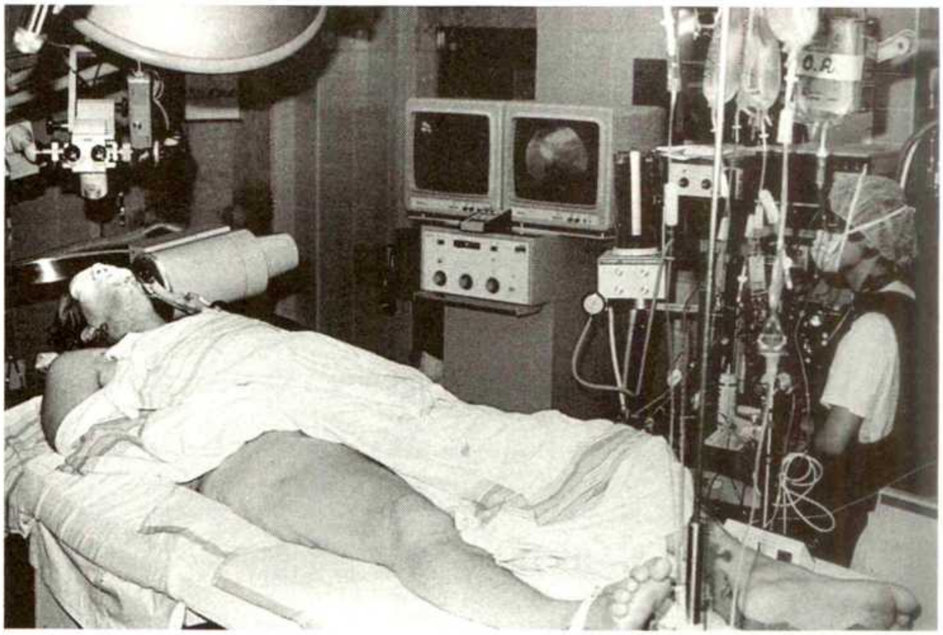

FIG. 3. Subject anaesthetized on the modified table.

clearing in the larynx. Although our patient exhibited none of these symptoms, it was felt that extra vigilance with regard to postoperative respiratory status would be a wise precaution.

A very real problem in this patient, however, was posed by the mechanics involved both in the safe transportation of such very large subject to and from the operating area, and in positioning her on a surgical table. For this purpose a standard operating table was extensively modified with regards to length, width and supporting structures (fig. 2). Because suitable padding was used, it also served the patient as a recovery room bed during her immediate convalescence (fig. 3).

The major problem encountered in the practical management of this patient was that of difficulty in tracheal intubation after the induction of anaesthesia. This was unexpected in view of two previously-documented uneventful intubations. At the time of her first craniotomy, the concentration of growth hormone was much higher, and at the time of this surgery, no symptoms or signs of upper airway obstruction were identified. Glottic visualization was difficult, not because of mucosal hypertrophy, but rather because the larynx was extremely anterior; possibly the trachea had been drawn forward by post-thyroidectomy scarring. In retrospect (and we would recommend this in other such patients), awake indirect laryngoscopy would ideally have been carried out before operation; the hazard might then have been anticipated and intubation managed by elective fibreoptic laryngoscopy. Blind intubation, although successful in this case, should be discouraged, because mucosal trauma may induce post-anaesthetic airway obstruction.

The potential difficulty of providing adequate ventilation proved unfounded in this case. The patient's normal tidal volume was 1300 ml; the Airshields ventilators used routinely in our hospitals can deliver a maximum volume of only 1400 ml, leaving little reserve for any unexpected increase in ventilatory requirement. In the event of such increased requirement, it was planned to ventilate the patient either manually with a special 5-litre reservoir bag or automatically with an M.A.I. volume respirator having the potential of delivering a maximal tidal volume of 2200 ml. We elected to substitute a circle system with optional in-line carbon dioxide absorber for the Bain circuit usually used in our hospital, since to ensure adequate respiratory exchange with the latter might necessitate fresh gas flows in excess of the capability of our flowmeters [14]. This arrangement provided adequate ventilation for the duration of the procedure without using the carbon dioxide absorber, and at the same time preserved the facility of using the nitrous oxide and enflurane supplementation.

Our patient was kept under close surveillance in the post-anaesthetic recovery room for 48 h, where her recovery was uneventful. The only complication was a transient period of diabetes insipidus, easily managed by administration of desmopressin.

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ENCLOSED AFFERENT RESERVOIR BREATHING SYSTEMS

Description and Clinical Evaluation

D. M. MILLER AND J. C. MILLER

SUMMARY

A new group of breathing systems, namely the Enclosed Afferent Reservoir (EAR) systems, is described. They allow for the selective elimination of alveolar gas in association with both spontaneous and controlled ventilation. A comparison with the Bain system in controlled ventilation demonstrates greater efficiency in eliminating carbon dioxide. A fresh gas flow ($\dot{V}_F$) of 70 ml kg^{-1} min^{-1} using an EAR system gave mild hypocarbia which equated to a $\dot{V}_F$ of 100 ml kg^{-1} min^{-1} using the Bain system. Smaller minute volumes of ventilation are required for optimal performance than with the Bain system. The minimum recommended minute volume of ventilation ($\dot{V}_I$) should equal $\dot{V}_F$ plus anatomical deadspace ventilation ($\dot{V}_D^{anat}$). The pattern of ventilation appears to have little influence upon the efficiency of carbon dioxide elimination when using an EAR system, whereas the Bain system does appear to be affected.

An afferent reservoir system can be defined as one which has a reservoir bag or reservoir facility on the inspiratory supply tube or afferent tube between the fresh gas supply and the patient. Examples of simple afferent reservoir systems are Mapleson A type systems: namely, Magill, Lack and Preferential Flow (PF) systems. Their unique advantage of efficiency in the use of fresh gas applies only to spontaneous ventilation. Conversely, efferent reservoir systems have reservoir capacity on the expiratory limb. These include all the "T systems", for example, Mapleson D to F. Their advantage of efficiency in the use of fresh gas only applies to controlled ventilation.

In order to secure the advantages of both the afferent and efferent reservoir systems, many combination systems are being introduced [1–7]. The advantages of the combination systems are now obtained with a single system, namely the enclosed afferent reservoir (EAR) system.

One of the main features of an ideal breathing system should inevitably be one which selectively eliminates alveolar gas in both spontaneous and controlled ventilation. Previously, the only system for which such a claim could be made was the "Circle H" system investigated by Eger and Ethans [8]. Unfortunately, the commercially available Circle H arrangement suffers from a number of serious disadvantages which Eger himself has pointed out: (1) it is somewhat bulky and slightly heavier than the simple Y-piece; (2) The valves are more difficult to see than dome valves; (3) The valves may "stick" on first use after a period of non-use. Opening these valves at this time may require considerable pressure; (4) Resistance to flow may be slightly greater than the resistance in dome valves; (5) Flushing with oxygen does not clear the inspiratory limb since inflow gases flow backwards.

Eger also claimed that, for Circle B, D and G arrangements, the same selective shunting out of alveolar gas could take place if the overflow valve was replaced with a Steen valve which closes with rapid increases in system pressure.

The newly introduced EAR systems, of which two types are described in this paper, also appear to have the property of selective alveolar gas elimination. These may be described as the "Enclosed Mapleson A" (EMA) and the "Enclosed Preferential Flow" (EPF) systems. The conventional Mapleson A system and its modifications have been shown to require a minimum

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fresh gas flow almost equal to the alveolar minute volume of ventilation during spontaneous ventilation [9–13]. During controlled ventilation the flow dynamics change completely as gas is eliminated from the system during the inspiratory phase instead of during the expiratory phase as in spontaneous ventilation. The EAR systems differ from Mapleson A type systems in that the expiratory valve is enclosed by connecting the exhaust outlet to a bottle which also encloses the afferent reservoir bag. The result is that pressurizing the bottle during the inspiratory phase of controlled ventilation squeezes gas from the afferent reservoir bag into the lungs and at the same time holds the expiratory valve closed so that expired gas is eliminated through the valve only during the expiratory phase. The same efficient shunting of gas fractions found during spontaneous breathing in Mapleson A type systems should, theoretically, now occur during controlled ventilation as well. Selective elimination of alveolar gas should, therefore, occur regardless of the mode of ventilation. This being the case, the EAR systems should be more efficient during controlled ventilation than the Bain system, since efferent reservoir systems cannot selectively eliminate alveolar gas [14]. Furthermore, the ability to maintain $P\mathrm{CO}_2$ by adjusting fresh gas flow should be improved and it should be possible to maintain $P\mathrm{CO}_2$ stable over a larger range of minute volumes. This may have clinical significance in those situations in which the large minute volumes of ventilation required for normocapnia in the Bain system may have an adverse effect on the cardiovascular system.

This investigation compared the EAR systems (namely the EMA and EPF) with the Bain system during controlled ventilation. The effect of different minute volumes of ventilation upon Pa_{CO_2} using the EPF and the Bain system was also studied. Finally, a comparison of the EMA and EPF systems was made.

Another investigation which evaluated minimum fresh gas flow requirements for spontaneous ventilation using a lung model has shown that the flow requirements of an EMA and an EPF system are similar to the Magill and PF Systems [15].

DESCRIPTION OF APPARATUS

The "enclosed Mapleson A system"

The system consists of a Mapleson A system enclosed within a non-distensible structure (fig. 1, upper diagram). The non-distensible structure may be considered in two parts. The first may consist of a bottle which encloses the reservoir bag A and the second a co-axially or parallel arranged tube which incorporates a one-way valve. A more practical arrangement (fig. 1, lower diagram) simply extends the expiratory tube to site the one-way expiratory valve in the bottle so that gas is vented into the latter. Other ports opening into the bottle include a means for positive pressure ventilation and a variable orifice.

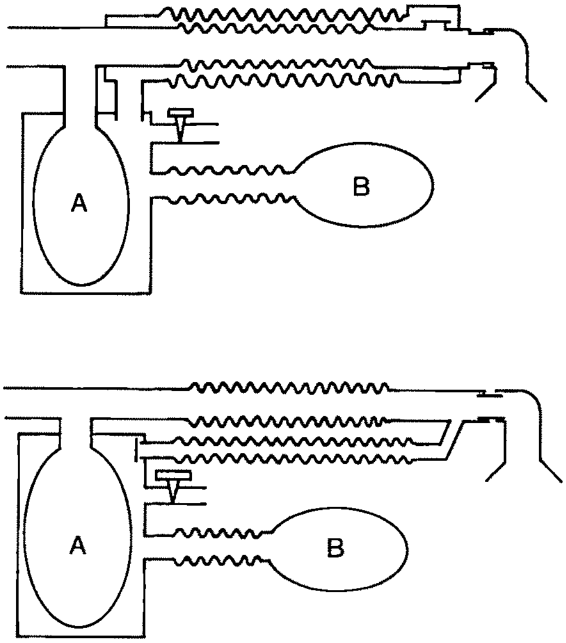

FIG. 1. Two versions of the enclosed Mapleson A system.

In operation during spontaneous ventilation, gas is vented from the system in a manner which is identical to the conventional Mapleson A system. In this mode of ventilation the variable orifice would be wide open. In controlled ventilation the variable orifice is partially closed to allow for a controlled leak from the bottle, while the reservoir bag B is squeezed intermittently. The movement of the various gas fractions during IPPV is no different from that during spontaneous ventilation. This is because the expiratory valve is held closed during the inspiratory phase by the inflating pressure within the bottle. This contrasts with the conventional Mapleson A system during IPPV when gas is vented through the valve during the inspiratory phase.

The enclosed "Preferential Flow System"

The EPF system may be considered in two parts: the fresh gas section and the exhaust gas section.

Fresh gas section. This section (fig. 2, upper diagram) consists of an arrangement similar to the Mapleson A system, except that the expiratory valve is replaced by a preferential flow T-piece which has a functional objective similar to that of the Heidbrink valve [3,13].

Exhaust gas section. This consists of a means by which the above section may be enclosed, as it were, "in a box" (fig. 2, lower diagram). This takes the form of a non-distensible corrugated tube co-axially arranged and a bottle enclosing the reservoir bag A as described above for the enclosed Mapleson A system.

In operation the only adjustment required is that of the variable orifice. This is opened maximally during spontaneous ventilation and partially closed during manual controlled ventilation. It is shut completely for mechanical controlled ventilation, when the ventilator is plugged into the bottle via the tube connecting the reservoir bag B. Excess gas is then disposed of through the ventilator spill valve.

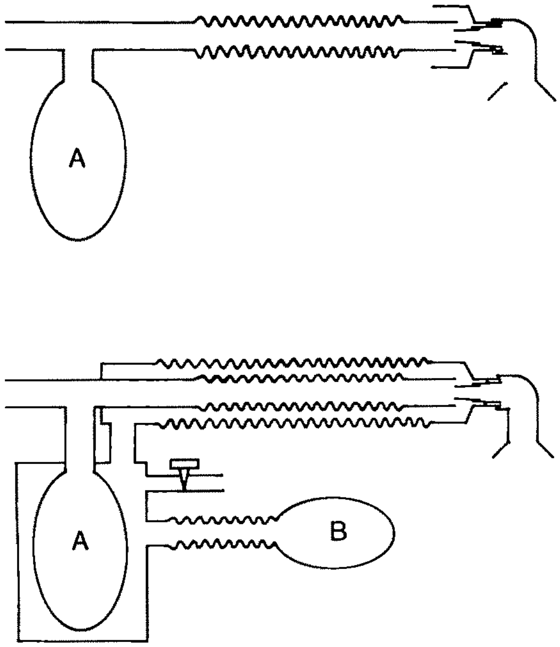

FIG. 2. The preferential flow system (upper diagram) and the enclosed preferential flow system (lower diagram).

The Variable Orifice (fig. 3)

This has been designed so as to have a sliding action, as opposed to the conventional screw mechanism of adjustment. This allows for quicker adjustment. The gradual taper on the plunger results in a gradual variation in the annular cross-sectional area of the orifice for a relatively large vertical movement of the head of the plunger. The position of the latter gives a clearly visible indication of orifice patency.

PATIENTS, MATERIALS AND METHODS

Permission for the study was obtained from the Ethical Advisory Committee. Consent was obtained from the patients for radial artery cannulation.

Patients selected were non-smokers, free of obvious pulmonary or cardiovascular disease and were classified as ASA grading I or II.

All patients not premedicated with an opioid were given one during the surgical procedure. Where indicated, a benzodiazepine was prescribed the night before surgery.

Evaluation of the systems during controlled ventilation was conducted on 27 patients. Most of the surgery was abdominal for an initial evaluation of 12 patients with several patients in the Trendelenberg position. For the study in the next 15 patients, using different tidal volumes, the need for very stable anaesthetic conditions was deemed necessary and surgery was restricted to orthopaedic and gynaecological procedures which combined general anaesthesia with an appropriate regional technique—such as brachial plexus block or caudal extradural block.

Anaesthesia was induced with a "sleep" dose of

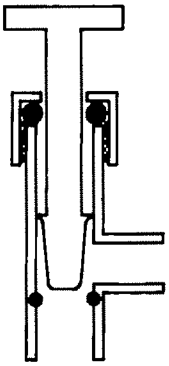

FIG. 3. The variable orifice.

thiopentone and intubation of the trachea was facilitated by topical anaesthesia, and the administration of an appropriate dose of alcuronium or suxamethonium.

A volume-preset ventilator with a bellows in the bottle arrangement was used. This comprised a constant flow generator (Bird Mark II) coupled to a Ventviva bellows in a bottle with an inspiratory time set for 1 s. The tidal volumes used were 10 ml kg^{-1} at a rate of 13 b.p.m. for the study on 12 patients using the three different systems: Bain, EMA and EPF. The I:E ratio was, therefore, approximately 1:3.5–1:4. The order in which the systems were used was randomized. For the next 15 patients the ventilatory rate was 13 b.p.m. and the tidal volumes used were 10 ml kg^{-1} followed by 7 ml kg^{-1} on each of the EPF and Bain systems. A calibrated Wright spirometer was used to measure expired tidal volumes. The systems were used in alternating order. Patients were kept adequately anaesthetized with nitrous oxide and halothane in oxygen. Appropriate doses of an opioid, and of alcuronium, were given as required.

A period of at least 30 min was allowed for stabilization before arterial samples were taken. Throughout the entire experiment a $\dot{V}\mathrm{F}$ of 70 ml kg^{-1} min^{-1} was used. A period of 20 min was allowed for stabilization after each adjustment had been made. All arterial blood samples were sent immediately to the laboratory once collected. Capnography was used in all patients to prevent undue increases in expired carbon dioxide during the lower minute volumes of ventilation.

An independent evaluation of the EPF and Bain systems was conducted in a different hospital on 17 patients. The design of the study and the methods were in all respects the same as for the investigation on the 27 patients except for the following differences. Ventilation was set on a Bird Mark 8 pressure-cycled ventilator with an anaesthetic circuit–ventilator volume of 2.5 litre [16], and a frequency of 10–12 b.p.m., with a tidal volume of 12–15 ml kg^{-1}. The duration of the inspiratory phase varied between 1.5 and 2 s. The inspiratory flow pattern to be expected when using a pressure generator such as the Bird Mark 8 was an exponentially decreasing inspiratory flow rate and resulted in an approximate I:E ratio of 1:2. Each circuit was studied as before with $\dot{V}\mathrm{F} = 70$ ml kg^{-1} min^{-1}. However, in 7 of the 17 patients time permitted further comparison using $\dot{V}\mathrm{F} = 100$ ml kg^{-1} min^{-1}.

RESULTS

Blood-gas analyses of Pa_{CO_2} on 27 patients comparing the EPF with the Bain system using $\dot{V}\mathrm{F}$ of 70 ml kg^{-1} min^{-1} and $\dot{V}\mathrm{E}$ of 130 ml kg^{-1} min^{-1} gave values (means and standard deviations) (SD) of Pa_{CO_2} of 4.77 ± 0.40 and 5.06 ± 0.37 kPa, respectively ($P < 0.001$): Student's paired *t* test).

A similar study by a different investigator was obtained on 17 subjects using the EPF and Bain systems and gave mean values for Pa_{CO_2} of 4.54 ± 0.54 and 5.14 ± 0.49 kPa, respectively. Using the same statistical analysis a significant difference between Pa_{CO_2} was again obtained ($P < 0.001$). Seven of the 17 patients were also studied using a fresh gas flow $\dot{V}\mathrm{F}$ of 100 ml kg^{-1} min^{-1}. The mean Pa_{CO_2} values were 4.00 ± 0.52 and 4.58 ± 0.60 kPa. The difference between the EPF and Bain systems was significant ($P < 0.005$).

In 12 of the 27 patients the EPF system was also compared with the EMA system and, as expected, no difference was found between the values of Pa_{CO_2} measured using these two similar systems (means and SD of Pa_{CO_2} were 4.84 ± 0.41 and 4.88 ± 0.45 kPa, respectively).

On the remaining 15 patients, a comparison of the effects of using $\dot{V}\mathrm{E}$ of 130 ml kg^{-1} min^{-1} on Pa_{CO_2} using the EPF and Bain systems gave Pa_{CO_2} values of 4.71 ± 0.40 and 4.95 ± 0.40 kPa for EPF and 5.01 ± 0.34 and 5.40 ± 0.44 kPa for the Bain system. The mean increases in Pa_{CO_2} resulting from the reduction in minute volumes were 0.24 and 0.39 kPa for the EPF and Bain system, respectively. From analysis of covariance it was found that this increase of Pa_{CO_2}, caused by the decrease in minute ventilation, was significantly less when using the EPF system ($P < 0.05$).

DISCUSSION

This study shows that the EPF and EMA are more efficient than the Bain system during controlled ventilation. This is ascribed to the means by which gas fractions are shunted so as to eliminate alveolar gas selectively. In addition, this view could be supported by the finding that smaller minute volumes of ventilation had less effect upon carbon dioxide elimination in the EPF than the Bain system.

It has been stated correctly by Conway [14] that selective elimination of alveolar gas does not take place with the Mapleson D system. The equation applicable to the Mapleson A system (only under the circumstances where $\dot{V}_F$ is equal to or less than the alveolar ventilation during spontaneous ventilation)

$$F_{A_{CO_2}} = \frac{\dot{V}_{CO_2}}{\dot{V}_F}$$

does not therefore hold for the Mapleson D arrangement. It should be noted, however, that in spontaneous ventilation with a Mapleson A system the $\dot{V}_F$ is too low if it is less than the alveolar ventilation.

Results obtained in this study would support the view that the selective elimination of alveolar gas occurs in controlled ventilation when using the EAR systems. The above equation can only be applied to breathing systems if certain conditions of minute volume of ventilation are fulfilled. The elimination of carbon dioxide in a system only becomes independent of ventilation when all of the fresh gas entering the system enters the alveolar space. This is the ventilation at which 100% utilization of the fresh gas takes place, which is likely to occur only in a system in which alveolar gas is selectively vented. With the Bain system this is unattainable in practice, as considerable gas mixing occurs within the system [17]. Rose and Froese [18] have shown that in clinical practice only 70–75% of the fresh gas enters the alveolar space using the Bain system. It was Conway [14] who correctly suggested that only infinite minute volumes of ventilation would achieve 100% utilization of fresh gas in the Bain system. In a perfectly functioning EAR system, however, these conditions would be fulfilled when the inspired minute volume ($\dot{V}_I$) = $\dot{V}_F + \dot{V}_D^{anat}$. In practice $\dot{V}_E$ was measured, and the small difference between $\dot{V}_E$ and $\dot{V}_I$ was ignored.

The EPF is not a perfectly functioning EAR system as it relies on mechanisms other than a valve to shunt gas in the appropriate direction. Nevertheless, the results do bear witness to improved economy during controlled ventilation when compared with the Bain system. For the EMA to be a perfectly functioning EAR system the valve needs to remain closed until the afferent reservoir bag is fully distended. If this were the case one would expect greater efficiency in utilization of fresh gas than with the EPF. This was not noticed. This could mean that either the EPF functions very efficiently or the EMA valve is not operating as it should. The fact that the Pa_{CO_2} increased by 0.24 kPa when the expired minute volume ($\dot{V}_E$) was decreased from 130 ml kg^{-1} to 90 ml kg^{-1} min^{-1} is accounted for by the fact that, for some patients, 90 ml kg^{-1} min^{-1} was probably less than the minimum $\dot{V}_E$ recommended, which is $\dot{V}_F + \dot{V}_D^{anat}$.

If the ratio $\dot{V}_D/V_T$ is 0.3, then $\dot{V}_E$ = 100 ml kg^{-1} min^{-1} when $\dot{V}_F$ = 70 ml kg^{-1} min^{-1}. Therefore, 100% utilization of fresh gas is probably only possible when $\dot{V}_E$ is greater than 100 ml kg^{-1} min^{-1}. In addition, since the EPF is not a perfect EAR system it may require—for optimal performance—a $\dot{V}_E$ greater than $\dot{V}_F + \dot{V}_D^{anat}$.

As the ceiling of efficiency is reached in the usual clinical range of minute ventilation in the EAR systems the regulation of Pa_{CO_2} by adjusting the fresh gas supply rate should, in theory, be more precise than that observed using the Bain system. This does appear to be the case in practice, as indicated by the significantly greater increase in Pa_{CO_2} in the Bain than the EPF system when using a lower $\dot{V}_E$ for ventilation.

The independent evaluation comparing the EPF and Bain systems showed a more marked difference in Pa_{CO_2}. This may be accounted for by the fact that the pattern of ventilation using a Bird Mark 8 ventilator does not favour the Bain system, tending to prolong the inspiratory phase and, consequently, shorten the total expiratory time. The total expiratory time includes the phase which Stenquist and Sonander [19] refer to as the time fraction for active expiration (F_{Et}) (although it is passive) and the pause phase. It is the pause phase which is shortened, since a change in the pattern of ventilation cannot usually alter the passive F_{Et} component of expiration. The pattern of ventilation with the Bain system appears to play a significant role in determining the degree of mixing of fresh gas with expired gas. This is consistent with what Stenquist and Sonander [19] have shown using a lung model—that the larger the time fraction for active expiration (F_{Et}), the greater the degree of rebreathing for a given $\dot{V}_F/\dot{V}_E$ value. Consequently, for a given rate of ventilation, the shorter the inspiratory phase, the longer the post-expiratory pause phase becomes, assuming that F_{Et}, which is passive, remains constant. A proportionately smaller ratio F_{Et}/total expiratory time is obtained and the efficiency of the Bain system is greater. The time-cycled constant-flow generator combined with a bellows in a bottle arrangement achieved a pattern of ventilation with an I:E ratio of about 1:3.5. This would allow for a longer pause phase than the study using a Bird Mark 8 with an I:E ratio of 1:2.

It seems likely, therefore that, in a system where alveolar gas is selectively eliminated, it is easy to achieve 100% utilization of fresh gas using minute volumes in the clinical range. In addition, the efficiency is not dependent upon the pattern of ventilation. However, the pattern of ventilation does appear to influence the efficiency of T-systems [19, 20].

Additional evidence supporting this claim for the EAR systems is illustrated in figure 4. A comparison of the inspiratory carbon dioxide pattern obtained from sampling in the tracheal tube during IPPV in a typical patient, using the two systems, is shown. The square-wave pattern can be seen using the EPF system, indicating the better fresh gas utilization and separation of gas fractions. In contrast to this there is an inspiratory hump of increased carbon dioxide tension, indicating the reinhalation of a mixture of alveolar gas with fresh gas when using the Bain system (fig. 4). Notice also that, when the tidal volume is increased from 800 ml to 1000 ml using the EPF, the inspiratory carbon dioxide value increases, but the record still stays flat and the square-wave pattern is retained. This would be consistent with the theory that simple addition of deadspace ventilation equal to the increase in minute volume of ventilation is what is occurring when $\dot{V}_E > \dot{V}_F + \dot{V}_D^{anat}$. Nevertheless, although the circumstantial evidence supporting this is strong, an experiment using a lung model would be necessary to prove this.

For spontaneous ventilation the EAR systems are not expected to perform in a manner significantly different from their simple afferent reservoir counterparts—Magill, Lack and PFS. This has been confirmed experimentally using a lung model [15].

An additional advantage discovered, as it were, by accident includes the possibility of built-in scavenging when the system is used for spontaneous ventilation. Suction may be applied directly to the expiratory port of the variable orifice with the reservoir bag B detached from the length of corrugated hosing. A continual flow of gas through the latter toward the suction tube provides for effective scavenging of the expired gases which are deposited into the bottle which behaves as a large reservoir. This is useful when no permanent scavenging system is available on the Boyle's machine.

Possible disadvantages include (as with the circle system) the inaccessible valve of the EMA system. It is for this reason that the EPF system is also presented here, since it is valveless. Both systems should, theoretically, produce even lower values of Pa_{CO_2} if they functioned perfectly. Valve function needs to be guaranteed and this is even more important if the suggested means of scavenging is to be utilized. It may be argued, however, that any slight negative pressure created by the scavenging suction, would be transmitted to both afferent and efferent limbs of the system and should, therefore, have no influence on the flow dynamics of the system.

Another possible disadvantage of such a system

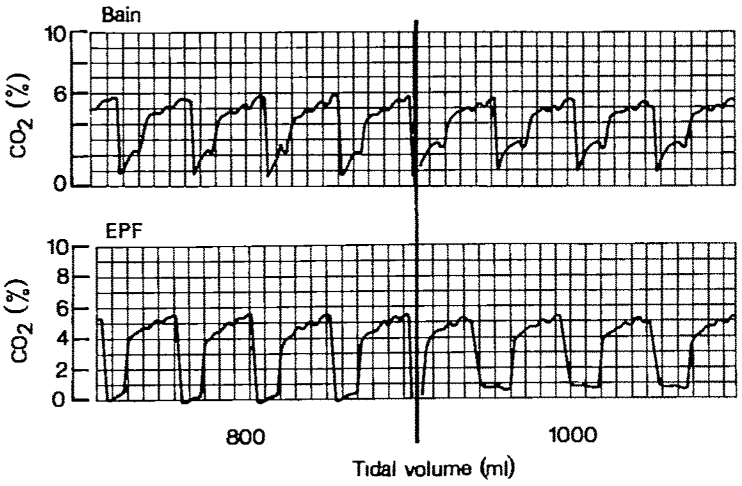

FIG. 4. Capnographic tracing of carbon dioxide sampling in the tracheal tube during IPPV with the Bain and EPF systems.

is that it could be considered bulky. However, if one realizes that the afferent reservoir bag-in-the-bottle arrangement takes the place of the ventilator bag, or bag-in-the-bottle, then the system is no more bulky than a combination A–D system.

In conclusion, a new group of breathing systems has been introduced, called the enclosed afferent reservoir systems. They are breathing systems in which the selective elimination of alveolar gas possibly takes place in association with both spontaneous and controlled ventilation. This results in a better control over Pa_{CO_2} and a greater efficiency in the use of fresh gas. Furthermore, the pattern of ventilation when using EAR systems appears to have little or no influence upon the efficiency of carbon dioxide elimination. The Bain system, however, does appear to be influenced by the ventilatory pattern. Accidental errors, which can occur when using combination breathing systems as a result of inappropriate use of Mapleson A or D mode, are obviated.

One small, but not insignificant benefit is the possibility for built-in scavenging to which the design lends itself. In addition, any unmodified ventilator with a power source other than the anaesthetic gases can be used with the system without any need for a bellows or bag-in-the-bottle arrangement, or a ventilator deadspace tube.

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CORRESPONDENCE

EMERGENCY CAESAREAN SECTION—TRACHEAL INTUBATION OR OESOPHAGEAL GASTRIC TUBE AIRWAY?

Sir—The correspondence from Tunstall [1, 2] on tracheal intubation in a 116-kg patient for emergency Caesarean section, for which an oesophageal gastric tube airway was used, prompts some comment on the original case report [3].

First the authors described "a larynx where the arytenoids and epiglottis could only just be seen" at laryngoscopy. In my experience this is neither an unusual nor an uncommon situation. Colleagues agree that they would expect to be able to introduce a tube in such circumstances and that they would have made a second attempt, particulary if the first attempt had been made by a trainee of lesser or little experience. This could have provided oxygenation most quickly with least delay, although an attempt to oxygenate with mask and oral airway (with the patient still supine) might be tried first.

Second, one must question the introduction of the head-down posture when, for a number of reasons, the patient could not be turned to the full lateral position. The management of the mask and jaw would be made more difficult, the greater weight applied to the diaphragm could have been responsible for the difficulty in ventilation, the increased venous pressure and associated venous congestion could have given the appearance of continuing cyanosis, and the risk of regurgitation from the stomach would be greater. At the same time, the relaxation of cricoid pressure, whether for the purpose of ventilation or intubation or for insertion of the oesophageal gastric tube airway, is surely unacceptable, since it exposes the airway to aspiration and soiling.

However, cricoid (and laryngeal) pressure can hinder, in addition to assist intubation, and the utmost care and supervision must be exercised in its correct application.

Also, in obese patients with a very short neck, it is worth trying more flexion or more extension of the neck to see if laryngeal visualization is improved. It may be easier to insert the laryngoscope with the head down and the neck extended, and I often use this manoeuvre in such patients when required to perform blind nasal intubation.

R. Williamson
Durban

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Sir,—Dr Williamson has rightly questioned the introduction of the head-down posture in the case report of an obese patient whose trachea could not be intubated and who had become cyanosed. An updated "failed intubation drill" indicates that, where positioning in the full left lateral posture is not possible, the next instruction in the sequence, to tilt the table head-down, is not implemented [1]. In this article [1] the various disadvantages of the head-down tilt are outlined. However, in the circumstances of the case report under discussion the anxiety caused by the possibility of stomach contents appearing in the pharynx, and being aspirated, produced a conditioned reflex response: the table was tilted head-down.

When cyanosis develops during a continuous but unsuccessful attempt to intubate the trachea, one cannot wait for a more experienced anaesthetist to appear. Patients without intubation difficulties in general present no problems for ventilation by bag and mask. On the other hand, where there is difficulty in intubating the trachea it is sometimes also difficult to ventilate the lungs by bag and mask.

Why do mothers continue to die, either from failure to intubate or from aspiration associated with difficult or failed intubation [2]? If, simultaneously with effective cricoid pressure, ventilation by bag and face-mask is always easy, in theory there should not be any deaths from hypoxia or aspiration associated with failed or difficult intubation.

In our case of failed intubation and similarly in the patient described by Boys [3], the airway was clearly improved when the tongue and epiglottis were displaced forwards by the oesophageal tube. In the absence of a correctly placed tracheal tube cricoid pressure should not be released completely unless the mother either is in a complete left lateral position (with head-down tilt) or has her oesophagus intubated with a cuffed tube. If the anaesthetist is uncertain if he has intubated the oesophagus, the tube should be pushed to the angle of the mouth, outside the face-mask, and bag-and-mask ventilation attempted. If the patient's colour improves, it confirms that the tube is in the oesophagus, where it had probably better be left *in situ*. It is then used as an oesophageal gastric tube airway.

M. E. Tunstall
C. Geddes
Aberdeen

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ANAESTHESIA FOR CAESAREAN SECTION

Sir,—The fascinating and erudite case report from Dr Redfern and colleagues [1] contains one surprising statement: that 67 % nitrous oxide was used during maintenance of anaesthesia for Caesarean section The work of Marx and Mateo [2] and Rorke and colleagues [3] has been widely accepted as indicating a need for maternal inspired oxygen concentrations in excess of 50 % to maintain optimal fetal oxygenation. In their discussion of the baby's poor condition at delivery the authors state that it is unlikely that the fetus was hypoxic when delivered. I disagree.

M. L. Heath
Lewisham

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Sir,—Dr Heath has pointed out a major error in our manuscript. We did indeed use 50 % nitrous oxide in oxygen until after the cord had been clamped, reverting to 67 % nitrous oxide only after delivery.

My apologies.

N. Redfern
Newcastle

PHARMACOKINETICS OF ATRACURIUM METABOLITES

Sir,—The report by Ward and colleagues [1] addresses important issues of pharmacokinetics of atracurium metabolites. The authors offer the conclusion that a prolonged infusion of atracurium 0.6 mg kg^{-1} h^{-1} will not produce plasma concentrations of laudanosine greater than the presumed safe ones. Although we deem the conclusion very likely, it was neither derived from, nor verified in, experiments, for the following reasons:

(a) Derivation of pharmacokinetic parameters for the metabolites of a drug administered by an i.v. bolus is based on the premise that no metabolites are present in the injection solution. Was this fundamental condition fulfilled?

(b) Molar, rather than metric, units are appropriate for the quantitative analysis of the metabolic conversions of a parent drug to its metabolites.

(c) The authors propose for the metabolites of atracurium "a standard two-compartment model with first order input from the atracurium plasma compartment". Does the proposed first order process describing the generation of a metabolite, $k_a.C$ in figure 2, allow for the generation of a metabolite commencing at zero amount formed at zero time and eventually generating more than one molecule of a metabolite from one molecule of atracurium? The first requirement must be true for any metabolite and the second arises from the consideration that there are two sites in the atracurium molecule that are susceptible to Hofmann elimination. In addition, the model in figure 2 implies that each of the two metabolites is generated independently from atracurium. The additionally imposed condition that the formation rate constant for each metabolite (k_a) equals the elimination rate constant of atracurium *in vivo* (β) leads, however, to an impasse. Were the latter condition true, formation of only one metabolite would fully and quantitatively account for the elimination of atracurium *in vivo* and would allow no room for the formation of the other metabolite. Hence, k_a for each metabolite must be smaller than β, and the sum of the formation rate constants for the metabolites cannot exceed the elimination rate constant for atracurium (β).

(d) Although computer-generated curves were fitted to the plasma concentrations of atracurium metabolites for individual patients (figs 3 and 5), the authors do not report either the solutions of the differential equations proposed in figure 2, or how well the models fit the results collected from all the patients (data in figures 4 and 6). Do the plasma concentration of laudanosine and the computer-fitted curve originate at 0 concentration at 0 time? What values did the authors obtain for V_1, V_2 and the macro- and micro-constants for each of the two metabolites?

(e) The definition of the "apparent clearance" is open to question. Since the numerator refers to the parent drug and the denominator to a metabolite, the ratio neither conforms to the definition of a clearance nor has any real meaning. At best, it represents an intermediate value to be used in further calculations. What, then, was the purpose of reporting these numbers (table V)?

(f) Is it justifiable to divide a hypothetical drug regimen (an infusion of atracurium was only assumed) by a parameter obtained using a questionable calculation (Cl_{app}), and then subject the data to statistical analysis using a variance and a t test? Moreover, the projected steady state plasma concentrations of laudanosine (table VI) amount to only 50 % of the values measured in patients treated with an infusion of atracurium at mean rates of 0.6 mg kg^{-1} h^{-1} or less during the first 24 h [2].

(g) The statement that "In the clinical environment the present study has shown that there are two significant metabolites in renal failure" is misleading. Since the generation of laudanosine and the alcohol is accompanied by the formation acrylates and acids (fig. 1), these other metabolites, although not measured in this study, may not be excluded from consideration. It remains to be seen which, if any, of the listed metabolites are "significant".

Unfortunately, we are left with the conclusion that the report by Dr Ward and his colleagues obfuscates rather than clarifies the issue of atracurium metabolites.

V. Nigrovic
S. Kidney
J. B. Pandya
Toledo, Ohio

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Sir,—The letter by Dr Nigrovic and his colleagues is an interesting combination of valid scientific criticism and failure to recognize important principles. Nevertheless, we shall attempt to respond, and apologize in advance to readers who are not well-versed in pharmacokinetics.

We were most careful not to make claims on safe plasma concentrations of laudanosine in man. Safety can never be presumed, but toxicity may be demonstrated. The quoted laudanosine plasma concentration of 17 μg ml^{-1}, causing convulsions in dogs [1] represented the best value known, but we concluded that it was unlikely to be reached by an intubating dose of atracurium or during prolonged infusions at the maximum recommended dose rate to patients with normal or impaired renal function. We find it scientifically inconsistent that Nigrovic and his colleagues support a conclusion while rejecting its derivation.

In response to the points raised in their letter:

(a) The injection solutions were not assayed for metabolites and we agree that this should be done for *all* pharmacokinetic studies. However, it appears that Nigrovic and colleagues interpret each metabolite profile (figs 4 and 6, from [2]) as an initial peak at approximately 2 min after the dose, from metabolite being present in the dosing solution; followed by a more sustained phase interpreted presumably as arising from plasma breakdown of atracurium and other precursors. This is not an unreasonable hypothesis, but we propose three arguments in reply.

First, the *amount* of metabolite in the dosing solution could only account for a small fraction of the *amount* measured in plasma at 2 min after the dose. Assuming that both compounds were confined initially to plasma, peak laudanosine would represent in excess of 3% and monoquaternary alcohol in excess of 8% of the 300 μg kg^{-1} dose, as minimum estimates. Quality control does not allow more than approximately 20% of these percentages of breakdown products to be present in atracurium besylate injection solutions and, therefore, we believe the greater portion of the early peak plasma concentrations of metabolites resulted from rapid initial breakdown of plasma atracurium.

Second, because the model fits each plasma profile from 2 min onwards, it might be argued that a "missing" portion from 0 to 2 min could be important. However, this "missing" area under the curve (AUC) represents an insignificant portion of the total since, citing laudanosine as the example, the maximum missing AUC (assuming the 0.19-μg ml^{-1} concentration had been constant for the first 2 min), would be 0.38 μg ml^{-1} min. Now the mean total AUC was approximately 30 μg ml^{-1} min (300 μg kg^{-1}/Cl_{app}, mean Cl_{app} = 10 ml min^{-1} kg^{-1}) (table V), and therefore any error arising from the missing early concentration would have been less than 2%.

Third, the model could easily accommodate metabolites being present in the dosing solution by simply making their *amounts* equal to X_1 at time zero (fig. 2).

(b) As molecular weights are known for all the chemicals discussed, it is simply personal preference whether molar or metric units are used. We have taken great care never to imply that pharmacokinetic analysis of this type could be used to quantify the absolute conversion of atracurium into any breakdown products.

(c) It should be clear from the discussion section of our paper on the metabolite pharmacokinetics that the intention of constructing the model was to "predict the behaviour of laudanosine... in situations outside those covered during the present study", and the particular choice of the "objective simplified model" allowed "a small objective constraint to be placed" for predictive purposes. This constraint forced a final exponential decline, defining a terminal half-life. Any model used for these purposes needs only to fit the observed data, and prediction beyond the original study is the sole test of the suitability of the model. A model is not a necessity; any curve-fitting method, for example moment or Fourier analysis, would have served equally well to predict steady state plasma concentrations of laudanosine arising from a long atracurium infusion. Dr Nigrovic and his colleagues have erred in over-interpreting a model which was clearly said to be "simplified" for two reasons:

First, the "proposed first order process describing the generation of a metabolite, $k_a.C$ in figure 2" does "allow for the generation of a metabolite starting at zero amount formed at zero time", although this condition is not related to the equation but to the initial condition (X_1 and X_2 set to zero at time zero). This was illustrated in figure 5, better for monoquaternary alcohol than for laudanosine in figure 3 because of the latter's compressed time scale.

Second, although the *numerical* value of k_a was set arbitrarily at 0.035, the first equation in figure 2 implies that k_a has the dimensions of clearance, and our use of mixed mass and concentration rate constants may have confused Nigrovic. Because only *concentrations* of metabolites can be measured, and not *amounts*, the relevant concentration rate constant, from the third equation, is k_a/V_1. *Only this ratio can be estimated by model-fitting the data, not the individual components.* Without an independent value of V_1, obtained from systemic metabolite dosing, a *completely free choice of either* $\mathbf{k}_a$ *or* V_1 (*but not both*) *may be made*, even if a choice of k_a implied the formation of 100 molecules of metabolite for each molecule of atracurium or a metabolite central compartment smaller than true plasma volume. This might be a wise choice, because any other "plausible" numerical value chosen might lead to a "plausible" volume of distribution which, if reported, would be interpreted mistakenly as a real value.

Dr Nigrovic and colleagues are correct in stating that matter must be conserved by the proposed breakdown scheme, but recognition of the indeterminate nature of k_a and V_1 (but not their ratio), resolves the apparent impasse While not affecting their argument, they have assumed, incorrectly, that the elimination rate constant is β. Even if atracurium followed standard two-compartment kinetics with removal only from the central compartment, β would be a hybrid of all the micro rate constants. It would only approach k_{el} (k_{10}), the true elimination rate constant, when there is very little two-compartment character to the kinetics—clearly not true for atracurium with $A = 18.7$ and $B = 4.9$ μg ml^{-1} mg^{-1} kg^{-1}.

(d) We did not report the solutions of the differential equations (fig. 2) because, as clearly stated in the legend to the figure, the computer package was used to fit the equations, and not the *solution* of the equations

The model was not used on the mean data (figs 4 and 6), although it may be, because we judged that a set of parameters for a "mean renal failure patient" was not appropriate.

The computer-fitted curves originated at zero concentration at zero time for both laudanosine and monoquaternary alcohol (MQA). The plasma concentrations of both compounds, measured immediately before administration of the dose, were always below detection limits.

The values for V_1 (V_2 was not defined, but the implication is understood) and the other micro and macro rate constants were not reported because, for the individual patients and both metabolites, this would have resulted in a table of perhaps 200 entries. We would invite Dr Nigrovic, or any other investigator wishing to have these values, to request them personally (B.C.W.).

(e) Dr Nigrovic and colleagues question the definition of "apparent clearance". The definition was given in the calculations section and the discussion section. The ratio has the dimensions of a clearance, and was deliberately called *apparent* to emphasize the point that the numerator referred to parent drug and the denominator to a metabolite. The purpose of reporting the parameter was to allow the reader to check the steady state calculation in the paper, to estimate the steady state plasma concentration of either metabolite from any constant infusion rate of atracurium, and to apply the methodology to other compounds. The definition and use of the "apparent clearance" parameter are therefore entirely valid, but Dr Nigrovic may wish to suggest a different *name* for the parameter.

(f) Dr Nigrovic and colleagues ask so many compound questions here, that for clarity it is necessary to re-state them:

Is it justifiable to predict a "steady state plasma concentration" by dividing a hypothetical infusion rate by the Cl_{app} as defined? Yes it is, making the single assumption that the pharmacokinetics of atracurium and metabolites are linear.

Is it justifiable to subject these calculations to statistical analysis? The tests were performed, knowing the degree of confidence that could be placed on results from the small sample sizes, to illustrate the uneven distribution of pharmacokinetic parameters and predicted values obtained from their arithmetical transformations. Regardless of any statistical interpretation, the clinically relevant interpretation should be to expect much more variability in steady state laudanosine concentrations during prolonged atracurium infusions to renal failure patients, than to patients with normal renal function.

Dr Nigrovic and colleagues state that "projected steady state plasma concentrations of laudanosine... amount to only 50% of the values measured in patients treated with an infusion of atracurium at mean rates of 0.6 mg kg^{-1} h^{-1} or less during the first 24 h [2]." If the relevant infusion rates were indeed 0.6 mg kg^{-1} h^{-1} or less, then the prediction would certainly underestimate by a factor of two, and the analysis would have been seriously flawed. However, the plasma concentrations from that study were known to us, and were considered not to contradict our predictions for the following reasons. First, the reported maximum laudanosine concentrations occurred during the later stages of the escalating atracurium infusions, when these rates had stabilized at values greater than the recommended maximum rate for surgical use. Therefore the laudanosine steady state predicted value needs to be calculated using the highest infusion rates of 0.71–1.43 (table I, from [3]), rather than 0.6 mg kg^{-1} h^{-1}, leading to an upwards revision by a factor of 1.2–2.4. Second, hepatic impairment in some of these patients would have led to higher values of laudanosine than predicted from renal failure alone, as mentioned in the final paragraph of our discussion.

(g) The statement "...the present study has shown that there are two significant metabolites..." cannot be misleading. We did not say that *only* two significant metabolites exist. It was judged unreasonable to speculate on the generation of monoquaternary acrylate and monoquaternary acid without reliable plasma measurements.

Finally, regarding the charge of obfuscation, the paper was a sincere attempt to report some experimental data and integrate them with previously published information on atracurium kinetics and dynamics. The construction of a model to allow prediction, outside the range of the study itself, of plasma concentrations that might have clinical relevance, should be preferable to reporting only average values, graphs and unchallengable assertions. We remain convinced that, until a relevant body of reliable experimental measurements becomes available, this experimental model can be applied to the pharmacokinetics of atracurium infusions.

B. C. WEATHERLEY
S. WARD
Beckenham

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HALOTHANE

SIR,—I was concerned to read the editorial on halothane by A. A. Spence [1]. The paper presents a biased and misleading view of the issues relating to halothane-associated hepatotoxicity, and makes no reference to published literature which supports the recent recommendations of the Committee on Safety of Medicines [2, 3]. The majority of anaesthetists would appear to concur with these recommendations [4–6].

A. W. ASSCHER
London

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SIR,—Professor Asscher must surely have been misled if he believes that the references which he cites [2–6] are in support of his Committee's recommendations. Stock and Strunin [2] concluded "repeated exposure to halothane in adult humans, particularly in obese, middle-aged women and over a short period of time (probably 4–8 weeks), may result in severe liver damage. However there is no means of predicting this, and the 'safe time interval' is unknown; the incidence of UHFH is probably of the order of 1 in 10000 anaesthetics. It is of interest that this figure is also quoted as the overall risk of deaths solely as a result of anaesthesia. .". The time interval of 4–8 weeks is taken from Neuberger and Williams [3]. Both publications recognize that, when repeated exposure to halothane is considered as a possible factor in hepatic necrosis, the intervals may be very long, extending to some years. The apparently arbitrary selection of 3 months as the specified interval by the C.S.M. is not obviously supported by either publication, or any other data published anywhere. The C.S.M. comment on the possible significance of pyrexia in the postoperative period stands without any obvious justification in the literature.

I accept that C.S.M. can draw support from the editorial by Dr Blogg [4] and from Anonymous [5]. Presumably, they missed the correspondence which followed Dr Blogg's editorial just as they have clearly misunderstood the letter from Professor Adams and his colleagues. In any case, I should be interested in Professor Asscher's definition of a majority.

C.S.M. has made a pronouncement which is bound to have a major impact on the practice of anaesthesia by virtue of their authority. They have made no obvious attempt to balance the risks of continuing and abandoning halothane. Worst of all, they failed to consult with the specialty of anaesthesia before going into print. These are the important issues, and these were the issues addressed in the Editorial.

A. A. Spence
Edinburgh

IMV AND WORK OF BREATHING

Sir,—We were delighted to read the paper by Mecklenburgh and colleagues [1], which is of great clinical interest to anaesthetists in intensive care units. The authors have shown that the increase in the work of breathing—as a result of the higher inspiratory resistance of the IMV circuit of Kontron 3100 ventilator—delayed the weaning of the patient from the ventilator. We would like to point out that the use of ventilators, such as the Bird IMV, which are capable of delivering continuous flow in the IMV mode, might be more advantageous in the clinical circumstances described by the authors.

The IMV Bird is fitted with a demand CPAP system which allows the installation of an automatic baseline compensator which, among many other functions, reduces the fluctuations in the baseline pressures observed whenever inspiratory demand exceeds inspiratory flow. This, therefore, significantly reduces the work of the breathing. This system is capable of giving inspiratory flow that is proportional to the inspiratory effort without altering the baseline pressures. Further, the Bird CPAP system was devised to reduce the work of breathing during IMV mode especially in the presence of PEEP. Most ventilatory devices provide a regulated positive end-expiratory pressure. However, during IMV procedures with PEEP, the patient may have to create substantial pressure gradients to entrain gases from the breathing circuit. This may significantly increase the work of breathing with resultant increase in oxygen consumption and carbon dioxide production—as might have happened in the case described by the authors. We do not know if the authors were using PEEP during weaning, which might have contributed to the difficulty in weaning. When all adjustments are made in the IMV mode in the Bird IMV system (including nebulization) which is done by an additional flow, there could be a continuous flow in the breathing circuit which might reduce the inspiratory resistance and, hence, work of breathing. The resistance of the humidifier may not be important in these circumstances.

Figure 2 of Mecklenburgh and colleagues shows an interesting finding. The slopes of A, B and C were similar, but that of D (alternate IMV) was less steep at higher flows compared with those of the ventilator circuits. Although the resistance of the ventilator alone (C) at lower flow rates was close to that of the IMV circuit, at a higher flow rate the difference between them appears to be substantial. This might suggest that the alternate IMV system was capable of delivering the higher flows required at higher inspiratory efforts more easily than the Kontron 3100 ventilator system used (inspiratory demand is better met by the inspiratory flow in the alternate IMV circuit than the ventilator). Therefore, the breathing characteristics of the alternate IMV system make it a more efficient circuit in the IMV mode than the ventilator itself. It would have been very interesting to see if the introducion of the humidifier to the alternate IMV system would increase the total resistance of the alternate IMV circuit by an anticipated 0.6 kPa or a value less than 0.6 kPa.

K. B. Shankar
H. Moseley
S. MacCoskie
Y. Kumar
Barbados

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Sir,—In response to the specific question posed by Dr Shankar and his colleagues, we were not using PEEP during weaning. While not necessarily agreeing with all the claimed advantages of the IMV Bird, we think that it undoubtedly true that, if PEEP is used during spontaneous ventilation, then gas must be available at an equal positive pressure during the inspiratory phase—unless the spontaneous breathing is to be assisted, or even deliberately hindered.

With regard to the last sentence of the letter: as we indicated in our paper (page 1052, column 2) it would not be sensible to include a humidifier in the alternative IMV system (since it is readily supplied with humidified gas).

The main message of our paper was not to extol the advantages of the alternative IMV system, but to show that the work of breathing through an IMV ventilator may be unduly and unnecessarily great.

J. S. Mecklenburgh
I. P. Latto
W. W. Mapleson
Cardiff

PULSE OXIMETRY DURING REPAIR OF CONGENITAL DIAPHRAGMATIC HERNIA

Sir,—A letter in your correspondence columns discussed the value of pulse oximetry during repair of congenital diaphragmatic hernia in a full-term neonate [1].

There are some debatable points in the letter, but the one which really cannot be overlooked is the statement that "management consisted of the continuation of dopamine, pancuronium and 100% oxygen" for the procedure. Whatever happened to the anaesthesia that the anaesthetist should have provided? How can the use of paralysis and oxygen alone for anaesthesia be condoned? In addition, one of the major objectives in the management of these patients is the avoidance of pulmonary hypertension, and it is well known that pain is a potent stimulus to pulmonary vasoconstriction. Pain also causes an increase in arterial pressure, and this must be a concern in these patients who are at risk of intracranial haemorrhage.

The use of moderate to high doses of narcotic agents has gained wide acceptance, especially where it is anticipated that the infant will require ventilatory support in the postoperative period, and I cannot see any reason for subjecting a small baby to the sort of treatment described by Dr Norman. I do hope that there was an error in his description of the management of his case, but it seems that neonates are not infrequently dealt with in that way.

E. C. Bloch
Durham, U.S.A

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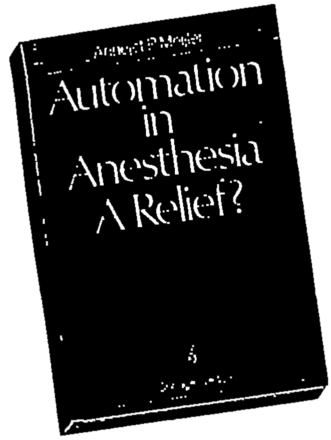

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M. P. B. Halmágyi, University of Mainz

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J. X. Brunner, G. Wolff, University of Basle

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J.-L. Vincent, Free University of Brussels,
L. G. Thijs, University of Amsterdam (Eds.)

Septic Shock

European View

1987. 76 figures, 50 tables. IX, 291 pages.
(Update in Intensive Care and Emergency Medicine, Volume 4)
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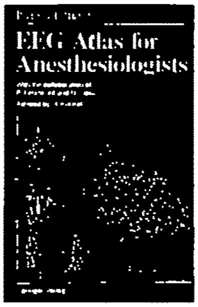

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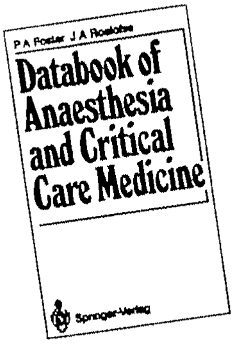
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W. J. Kox, D. J. Bihari,
London (Eds.)

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1987. 89 figures. 256 pages
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